

INNOVATIONS

in Urology



Urologists Turn from Volume to Value pg 4

Do green tea polyphenols slow prostate cancer? pg 3

A novel approach to treating childbirth-associated urinary incontinence pg 7

A new working group for pediatric urologic oncology pg 8



University Hospitals Case Medical Center and Case Western Reserve University School of Medicine are consistently recognized as two of the premier institutions in the nation, according to U.S. News & World Report's annual rankings.

Chairman's Corner

Facing the Health Care Climate of Change



From time to time during my career, I have witnessed our resiliency as urologists in overcoming perceived threats to our profession, such as the advent of managed care or that of robotic/laparoscopic surgery. Each time, urologists have stepped up, met the challenges and adapted. So today, urologists are faced with the question, "What will happen to my practice as a result of the Affordable Care Act?" And just as it has been in the past, the answer is that we will do what is best for our patients. This invariably will involve less invasive treatments, a reduction in health care costs and a higher quality of care.

In this Winter 2014 issue of Innovations in Urology, you will read about the leadership role urologists can play in our profession, simply by leading the discussion within our own urologic community. We also highlight how urologists at University Hospitals Urology Institute are leading within our areas of urologic expertise with the inception of the Pediatric Urologic Oncology Working Group and coordinating care among multidisciplinary experts within the Female Pelvic Medicine & Surgery Center.

You will also read about two exciting clinical trials that we have initiated and for which we are actively recruiting. One trial will assess the use of green tea extracts to slow the progression of prostate cancer during active surveillance. The other is a Phase I trial that begins our

clinical research into the use of stem cell transplantation to enhance tissue repair after childbirth, and prevent long-term incontinence.

I hope that the articles in this issue inspire you. And as always, I look forward to hearing from you with any comments, questions or suggestions.

Warm Regards,

Firouz Daneshgari, MD
Chairman, Department of Urology
University Hospitals Case Medical Center
Director, UH Urology Institute
Lester Persky Professor and Chair
Department of Urology
Case Western Reserve University School of Medicine



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National Institutes of Health (NIH) funded research is awarded to the School of Medicine at Case Western Reserve University.

Beyond Waiting

Antioxidant polyphenol trial for prostate cancer begins enrolling patients



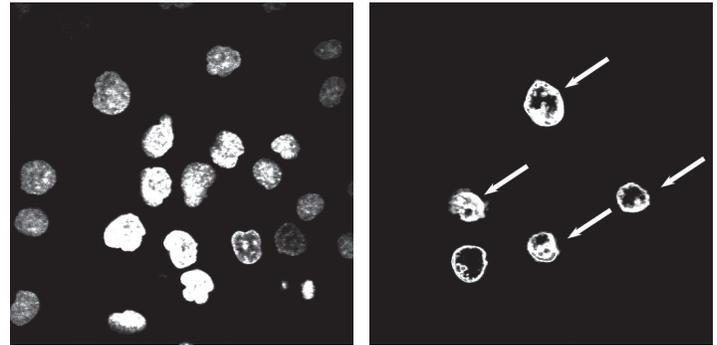
Robert Abouassaly, MD, MSc, Urologic Oncology & Minimally Invasive Therapies Center, UH Case Medical Center; and Assistant Professor, Case Western Reserve University School of Medicine

Prostate cancer is often slow-growing and for some will never advance significantly. Over 90 percent of the men diagnosed with prostate cancer have localized disease, typically with PSA levels lower than 10 ng/mL. And an estimated 50 to 75 percent of men with prostate cancer will die of other causes. Given the adverse effects of aggressive treatment, such as incontinence and sexual dysfunction, the trend in low-risk disease is to employ active surveillance rather than begin with aggressive therapy to try to eradicate the disease.

Men with disease that is appropriate for active surveillance will often undergo prostate-specific antigen (PSA) screening, regular digital-rectal exams (DREs) and sometimes biopsies, with the more aggressive treatment options reserved for patients whose cancer progresses. But knowing that one has any cancer, even a slow-growing disease, compels most men to want to do more than simply wait. “Men often ask us if there is some kind of dietary change that they can make, but there is no clear evidence for any effects of diet on disease progression,” says **Robert Abouassaly, MD, MSc**, Urologic Oncology & Minimally Invasive Therapies Center, University Hospitals Case Medical Center; and Assistant Professor, Case Western Reserve University School of Medicine. “There is a real need for something that patients can actively do.” Green tea polyphenols have gained interest for possible anticancer properties as a result of epidemiological studies showing rates of certain cancers are much lower in individuals who consume large amounts of green tea.

Phase II Study Begins

This phase II trial will investigate the efficacy of oral Sunpheron®90DCF-T, a green tea extract that contains over 80 percent epigallocatechin gallate (EGCG), an important antioxidant polyphenol. Preclinical studies using prostate cancer cell lines conducted by **Sanjay Gupta, PhD**, Carter Kissell Professor and Research Director, Department of Urology, Case Western Reserve University School of Medicine, and colleagues, show that EGCG induces apoptosis in cancer cells. Other studies conducted by Dr. Gupta and colleagues demonstrated that EGCG down-regulates growth factor expression, reduces cell proliferation, and suppresses cancer in a prostate cancer mouse model.



Prostate cells' *in vitro* response to epigallocatechin gallate (EGCG)

The trial's primary investigators are Dr. Gupta, Dr. Abouassaly, and **Lee E. Ponsky, MD**, Director, Urologic Oncology & Minimally Invasive Therapies Center, UH Urology Institute, Leo & Charlotte Goldberg Chair in Advanced Surgical Therapies, UH Case Medical Center; and Associate Professor, Case Western Reserve University School of Medicine. The study will investigate Sunpheron 400 mg QD compared with placebo in 48 men. All subjects will have five visits over the 52-week study, with the option for those who have positive results to continue under a long-term follow-up. Sunpheron has already been tested in a Phase I trial in healthy adults. Adverse events with 800 mg doses were predominantly mild with uncommon cases of moderate headache and no severe adverse events.

“We are definitely interested in enrolling patients who qualify for the trial and are excited about offering this option to men who have low-risk prostate cancer and are under active surveillance,” says Dr. Abouassaly.

Enrolling Patients

The Phase II Trial of Green Tea Extract has begun enrolling men with low-risk (T1 or T2) prostate cancer. For more information, please contact Dr. Abouassaly at **216-286-6617**.

Leading the Discussion

In the wake of the Affordable Care Act, urologists turn from volume to value



Firouz Daneshgari, MD, Director, UH Urology Institute, UH Case Medical Center; and the Lester Persky Professor and Chair, Department of Urology, Case Western Reserve University School of Medicine

With the signing of the Affordable Care Act (ACA) in 2010, physicians and payers around the country have been focused on transforming the health care system into a more streamlined and affordable model with quality of care as a priority. Within this new paradigm, it is critical that urologists engage in a discussion of what this will mean for urological care in the future.

The key feature relevant to physicians and payers has been improving care in a cost-efficient manner. "Urologists need to be informed on what the transition from a volume-based service to a value-based service really means in practice," says **Firouz Daneshgari, MD**, Director, University Hospitals Urology Institute at UH Case Medical Center; and the Lester Persky Professor and Chair, Department of Urology, Case Western Reserve University School of Medicine.

As part of its obligations under the law, the Centers for Medicare and Medicaid Services (CMS) is developing a new model for reimbursements initiated through Medicare, but the key concepts are already being implemented among private payers. Although

fee-for-service is still available with Medicare, new options including bundled or global-payment-based reimbursements are being implemented, as well as shared savings programs for accountable care organizations (ACOs). The latter are groups of health care providers that join together to give coordinated care to Medicare patients. The concept was initiated in answer to data showing that when care is not coordinated across providers, services are often duplicated and medical errors are more likely. With ACOs, physicians stand to share in the savings when certain quality standards are met with lower expenditures (i.e., fewer or less costly procedures and fewer patient encounters).

Defining Quality Outcomes in Urology

Given the changes that are occurring across all fields of medicine, the challenge is for urologists to engage in the discussion and help define the quality standards for the most common urologic conditions. Under the current payment system, physicians are rewarded financially for choosing procedures that are the most overvalued in the



Sirin Koroukian, PhD; Firouz Daneshgari, MD; Robert Aboussaly, MD; and Matthew Maurice, MD

Medicare diagnosis-related group (DRG) system; in other words, those that are reimbursed at a rate that is higher than the typical cost. In the new system, physicians receive the most benefit when they are able to achieve a predetermined patient outcome using fewer resources.

“The question that we as urologists need to be asking is, ‘Given a particular condition, which treatments will most cost-effectively achieve the desired patient outcomes?’” says Dr. Daneshgari. For example, in a case of urinary incontinence and overactive bladder, if the outcomes being targeted are patient satisfaction and quality of life with reductions in cost, then the optimum care will directly aim for these measures. This may mean forgoing urodynamic testing and cystoscopy, and instead treating with onabotulinumtoxin A injections, which will likely reduce procedural and visit-related costs while improving the patient’s quality of life.

“Even though some urologists may already be targeting quality outcomes while maintaining cost efficiency, the current system doesn’t reward them for this practice,” says Dr. Daneshgari. Instead, it rewards physicians who do more procedures. But the new model of reimbursement would allow physicians who are part of an ACO to share in the savings.

ACOs and the Urologist

Depending on their employment status, urologists will find themselves either automatically part of an ACO or, if they are independent, with the option to form or join an ACO (**Figure 1**). “Most large academic centers are already set up as ACOs, so urologists employed by them are included in the ACO,” explains Dr. Daneshgari.

Within the ACOs, defining the quality standards will invariably be decided by the specialist members for each condition or disease (**Figure 2**). “As urologists, we will be called upon to help determine what the target outcomes will be for common conditions we treat,” says Dr. Daneshgari. For prostate cancer, for instance, the outcomes might be based on cancer-free survival at five years and biochemical (prostate specific antigen) recurrence status. Given these target outcomes, a urologist would base treatment decisions on the available evidence in the literature to optimize these outcomes while reducing expenditures. “We know that aggressive surgical treatment in prostate cancer does not add to longevity,” explains Dr. Daneshgari. “Overall, we will continue to see a significant shift towards nonsurgical treatments.”

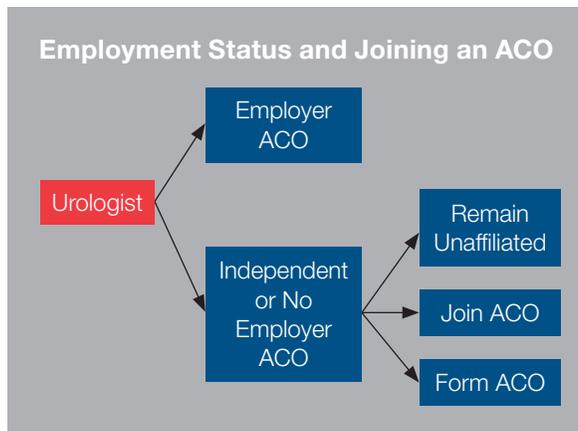


Figure 1

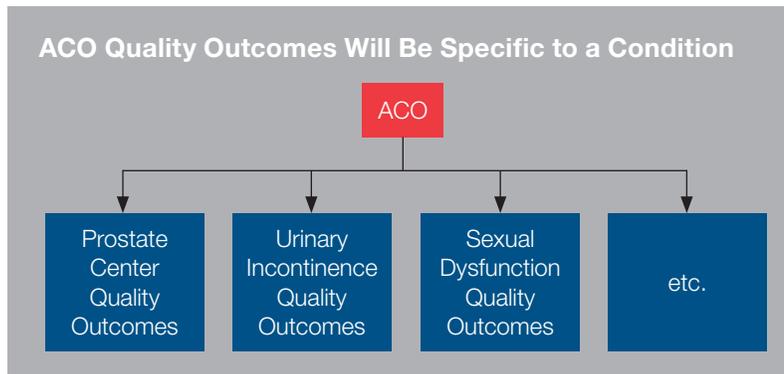


Figure 2

As a leader in the field, Dr. Daneshgari sees the need for urologists to define their place in the progression toward value-based care. “Whether actively joining an ACO or being a part of one based on employment status, we have an obligation and opportunity to offer our expertise in defining quality care within our specialty,” says Dr. Daneshgari.

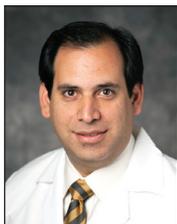
Outcomes-Focused Urologic Care

For patient referrals and appointments, call **1-866-UH4-CARE**. To speak with one of our specialists directly, call **216-844-3009** or email **UroInnovations@UHhospitals.org**.

Innovative Treatment

A Unique Model of Multidisciplinary Care

Finding solutions and improving quality of life for women with pelvic floor disorders



Adonis Hijaz, MD, Director, Female Pelvic Medicine & Surgery Center, UH Urology Institute, UH Case Medical Center; and Associate Professor, Case Western Reserve University School of Medicine

An estimated 36 percent of American women suffer from at least one female pelvic floor disorder (FPFD), such as urinary incontinence (UI), fecal incontinence or pelvic organ prolapse. Although the prevalence of FPFDs increases with age, one-fourth of women between the ages of 25 and 39 have reported symptoms. The Female Pelvic Medicine & Surgery Center at University Hospitals Urology Institute has taken on the challenge of providing comprehensive care for women with FPFDs.

“Given the number of specialists who may be called upon to develop an effective treatment plan for a particular patient, we sought to simplify the process by creating the Female Pelvic Medicine & Surgery Center,” says **Adonis Hijaz, MD**, Director, Female Pelvic Medicine & Surgery Center, UH Urology Institute, UH Case Medical Center; and Associate Professor, Case Western Reserve University School of Medicine. The center brings together urologists, urogynecologists, colorectal surgeons and nurse practitioners, as well as urodynamic technicians, specialized physical therapists and psychologists, under one roof. “It is rare to have a center that is a physically cohesive entity,” explains Dr. Hijaz. Many centers that focus on FPFDs are described as such on paper but do not actually have a centralized location, and often the team of health care professionals would not be considered multidisciplinary.

To improve the quality of life for a patient with an FPFD, it is essential to understand the interrelated conditions that underlie the disorder. “It’s less about new techniques and more about innovative thinking,” says Dr. Hijaz. “Each individual specialist has something to offer, but it is the combination of expertise that is helping us make the best advancements.”

The Importance of Research and Outreach

Surgeon-scientists at the UH Urology Institute have developed a culture that stimulates innovation in improving treatment and care to patients. Using



Combining Disciplines to Address Pelvic Pain

The UH Urology Institute now offers an interdisciplinary fellowship focused on pelvic pain, which combines training in anesthesiology, pain management, gynecology and urology. The fellowship, one of only a few of its kind in the country, is designed to bridge the gap in knowledge among these disciplines and develop a new generation of specialists in FPFDs.

“We are excited to offer this training because despite our best efforts, none of the individual specialties really provides a well-rounded approach to female pelvic pain,” says Dr. Hijaz. Because many cases of pelvic pain stem from tissue damage sustained during childbirth, the collaboration of these four disciplines promises to provide a unique approach to treatment and management of this condition.

inspiration gained through the multidisciplinary interactions in the clinic setting and creating well-designed studies to investigate solutions is an integral part of the job.

One recently initiated study focuses on UI associated with childbirth and the possible key risk populations, such as women with gestational diabetes, advanced maternal age and obesity. The prospective study involves collaboration with the UH Labor and Delivery Department to evaluate any correlations between potential clinical biomarkers and the development of UI. Results of this study could help predict which patients will benefit from early intervention to treat postpartum UI.

Another series of investigative studies involves using stem cells to drive postpartum tissue repair to prevent UI. The work for this research, an example of the bench-to-bedside model, began with laboratory studies, and a clinical trial is expected to launch in 2014 (see page 7).

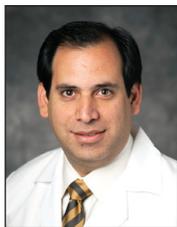
Having an investigative mindset helps surgeon-scientists discover new and improved modalities of care. This is exemplified in the joint outreach program between UH Urology Institute and the Center for Geriatric Medicine to provide on-site care to elderly individuals living in senior residences. This initiative was designed to address undertreatment of common urological conditions in elderly women, such as UI, recurrent urinary tract infections and overactive bladder. The nationally recognized program not only improves the quality of life among the patients, but also has had a measurable positive impact on health care resources.

Bench-to-Bedside

New hope for childbirth-associated urinary incontinence



Firouz Daneshgari, MD, Director, UH Urology Institute, UH Case Medical Center; and the Lester Persky Professor and Chair, Department of Urology, Case Western Reserve University School of Medicine



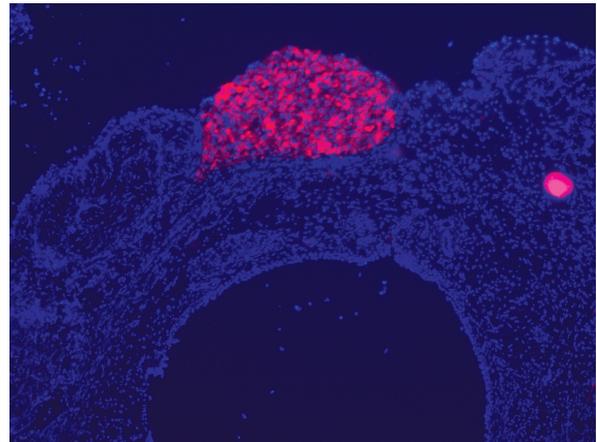
Adonis Hijaz, MD, Director, Female Pelvic Medicine & Surgery Center, UH Urology Institute, UH Case Medical Center; and Associate Professor, Case Western Reserve University School of Medicine

Stress urinary incontinence (SUI) is a relatively common problem for women following childbirth, with the greatest risk associated with obesity, diabetes and advanced maternal age. Typically SUI resolves in the weeks after childbirth as tissues of the pelvic floor heal from the trauma of childbirth. However, an estimated 91 percent of women who have UI three months following childbirth will continue to have UI long-term. In 2014, University Hospitals Urology Institute will initiate a clinical trial to study the efficacy of stem cells to enhance pelvic tissue healing.

Although stem cells may be embryonic, several types of stem cells are maintained in adult tissues, such as bone marrow. Adipose tissue acts as a good source of stem cells as well. The benefit of all stem cells is that they are undifferentiated and can be stimulated to evolve into many different types of cells. But adipose stem cells (ASCs) have been embraced for their ability to enhance healing rather than their ability to differentiate into newly functional cells. When placed in a tissue, they often respond by producing specific soluble factors, such as cytokines or growth factors, that stimulate cell growth and healing. **Firouz Daneshgari, MD**, Director, UH Urology Institute, UH Case Medical Center; and the Lester Persky Professor and Chair, Department of Urology, Case Western Reserve University School of Medicine; and **Adonis Hijaz, MD**, Director, Female Pelvic Medicine & Surgery Center, UH Urology Institute, UH Case Medical Center; and Associate Professor, Case Western Reserve University School of Medicine, recently completed preclinical work in developing a methodology for using ASCs to enhance tissue repair in a rat model of UI. "The preclinical work provided the impetus to apply for a stage 1 clinical trial," says Dr. Daneshgari.

At the Bench

One of the first steps Drs. Hijaz and Daneshgari took was to develop the rat model that could be used for stem cell transplantation studies. "We began by creating the rat model that would allow us to properly develop the technique and assess the effects of ASCs on pelvic floor damage," says Dr. Hijaz. He and his colleagues published those results in 2009. Then they worked to develop the implantation technique and study the effects of implantation on cytokine production in the rat model. "The results of the work in the animal model were extremely encouraging," says Dr. Daneshgari.



Fluorescent PKH-26 labeled human Mesenchymal Stem Cells (red) coalesced in the rat urethral tissues (DAPI-blue) 24 hours after periurethral injection of the cells. The internal circle is the lumen of the urethra.

To the Bedside

Drs. Daneshgari and Hijaz are in the process of obtaining FDA approval to begin the Phase I clinical trial, which will probably commence in 2014. Unlike what is customary for stem cells used for bone marrow transplants, the ASC procedure that will be used in this study will not require harvesting followed by *in vitro* culture before implantation. "It will be based on a point-of-care procedure, meaning the ASCs will be collected via liposuction, minimally manipulated, and then implanted during a single visit to the surgical center." This study marks the critical step of translational science – bringing innovation from the laboratory bench to the clinical bedside – the ultimate goal of surgeon-scientists who are truly passionate about improving patient care.

For More Information:

To request a patient referral, contact the Female Pelvic Medicine & Surgery Center at **216-844-3009** or email **UroInnovations@UHhospitals.org**.



Innovative Collaborations

Research and Education in Pediatric Urologic Oncology

Inaugural working group formed to drive solutions



Jonathan H. Ross, MD, Director, Pediatric Urology Center, University Hospitals Urology Institute and UH Rainbow Babies & Children's Hospital; and Professor, Case Western Reserve University School of Medicine

Because urologic cancer in children is rare, it can be difficult for researchers and clinicians to study and gain treatment experience. However, this experience may be crucial to obtaining good treatment outcomes. Fortunately, experts in pediatric genitourinary (GU) cancers have a strong history of networking and collaborating to ensure that clinicians across the country have treatment support, and that experience gained with individual cases is carried forward in developing best practices.

This past September at the Pediatric Urology Fall Congress in Las Vegas, a new collaboration known as the Pediatric Urologic Oncology Working Group met for the first time under the auspices of the Society for Pediatric Urology (SPU). The group's inaugural president is **Jonathan H. Ross, MD**, Director, Pediatric Urology Center, University Hospitals Urology Institute and UH Rainbow Babies & Children's Hospital; and Professor, Case Western Reserve University School of Medicine. Previously, leaders in pediatric urologic oncology met at the American Academy of Pediatrics (AAP) annual conference. "The new working group will replace and expand the previous group to foster the discussion and study of pediatric urologic cancers among our colleagues. Any interested member of the SPU is welcome," explains Dr. Ross.

Bringing Together Clinicians and Researchers

The Pediatric Urologic Oncology Working Group serves three missions: education, pediatric urology participation in the Children's Oncology Group (COG), and development and support of multicentered surgical research. "One mission will be to help educate pediatric urologists and others about these tumors through talks at national meetings and by responding to requests for advice about treatment," says Dr. Ross.

At the recent Fall Congress, an educational panel discussion was held on the pros and cons of minimally invasive surgery in the management of renal tumors in children and adolescents. The panel discussed

minimally invasive surgery as a combination treatment with preoperative chemotherapy and its role in older children or adolescents with Wilms' and other renal tumors. (In the Fall 2013 issue of *Innovations in Urology*, we highlighted the treatment of a case of bilateral Wilms' tumor by Lynn Woo, MD, Pediatric Urologist, UH Urology Institute; and Assistant Professor of Surgery, Case Western Reserve University School of Medicine.)

The COG is an international clinical trials group supported by the National Cancer Institute. It includes more than 8,000 experts and more than 200 academic centers from around the world. "Our working group will help support GU cancer interests of the COG," says Dr. Ross. "Many of the working group organizational committee members are also members of COG."

The third and key mission of the new working group will be to develop and support multicenter trials for pediatric urologic tumors, since collaboration is key to obtaining adequate treatment and management evidence. Members of the working group will generally meet twice a year, at the Pediatric Urology Fall Congress and at the SPU/American Urological Association (AUA) subspecialty society meeting. "During the biannual meetings, the members of the working group will have the opportunity to design and present protocols that we will collaborate on and carry out," says Dr. Ross. "Surgical techniques play a key role in treating many of these cancers, which makes the collaboration among pediatric urologists for these studies particularly important."

Management Advice

For management questions regarding pediatric urologic tumors, visit spuonline.org/GU-Tumors-Resource.cgi or contact Dr. Ross directly: Jonathan.Ross@UHhospitals.org