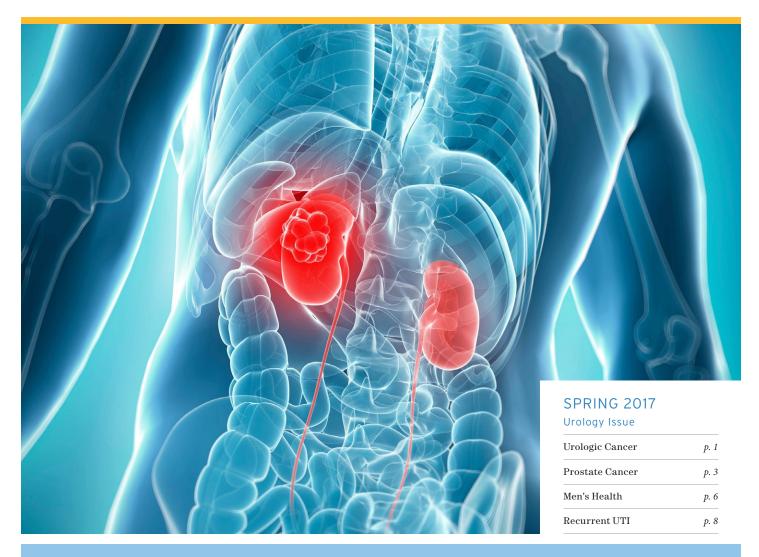


Physicians Update





UROLOGIC CANCEL

New Chemo Vector Offers Option for Patients with Difficult to Treat Urologic Cancer

UCLA researchers have reported promising results in preclinical studies of a new approach to treating upper-tract urothelial cancer, with the potential to improve the delivery of chemotherapy drugs to their target, minimize side effects and substantially reduce the number of patients who lose a kidney as part of their treatment.

Urothelial carcinoma, or cancer of the lining of the urinary tract, is most common in the bladder but also can occur in the tubes that connect the kidney to the bladder, as well as in the urinary-tract lining within the kidneys themselves. The kidney is composed of the "meat" and the "sink." The "meat" of the kidney filters the blood and drains the waste

 $continued\ on\ p.\ 4$

UCLA Clinical Updates

Learn about the Latest Advances from UCLA

MR-Targeted Biopsy in Prostate-Cancer Diagnosis

Targeted MR-guided biopsy via either magnetic resonance-ultrasound (MR-US) fusion or direct MR-guided biopsy is emerging as the best way to detect, grade and stage prostate cancer.

UCLA Fetal Care Program

The UCLA Fetal Care Program provides comprehensive, state-of-the-art screening, monitoring and medical management of high-risk pregnancies before, during and after delivery. With UCLA's NICU adjacent to labor and delivery, newborns can immediately receive full medical and surgical treatment, while mothers can remain close to their babies.

Preserving Childbirth Options in Female Cancer Patients

The UCLA Department of Obstetrics and Gynecology includes a team dedicated to counseling reproductive-age patients facing imminent cancer treatment and to devising a plan for fertility preservation. Fertility preservation may also benefit women with other conditions affecting reproduction.

California Rehabilitation Institute

A partnership among UCLA Health, Cedars-Sinai and Select Medical has created the largest inpatient physical medicine and rehabilitation hospital on the West Coast.

Pediatric Epilepsy Surgery

While medication can control seizures in the majority of pediatric epilepsy patients, epilepsy surgery remains an underutilized option that can be highly successful in treating carefully selected children with medical-refractory seizures.

High-Intensity Focused Ultrasound for Prostate Cancer

UCLA's Department of Urology offers a new, minimally invasive alternative for treating prostate cancer. HIFU destroys diseased prostate tissue by delivering ultrasound energy, not radiation, to the targeted tissue without the need for an incision.

UCLA Dementia and Memory Disorders Clinic

UCLA is committed to providing quality care for people with all types of dementia through a rigorous diagnosis protocol, an active and expanding clinical trials program, and a focus on basic and translational research.

UCLA General-Surgery Practice Opens in Northridge

The UCLA Department of Surgery recently expanded into the San Fernando Valley and opened a new general-surgery practice in Northridge.

UCLA Orbital Disease Center

The Orbital Disease Center of the UCLA Stein Eye Institute is one of only a handful of institutions in the United States to offer a dedicated orbital-disease center.

Integrated Approach for Children with Thyroid Problems

UCLA's Pediatric Thyroid Program is one of the few centers in Southern California that specializes in the diagnosis, treatment and care of children with all types of thyroid problems, including thyroid nodules, thyroid cancer and other thyroid disorders.



To download these and other clinical advances at UCLA Health, go to: uclahealth.org/clinicalupdates







News from UCLA Health

Link Between Inflammation and Prostate-Cancer Risk

UCLA researchers have discovered a previously unrecognized type of progenitor cell that is found in uncommonly high numbers in inflamed areas of the prostate gland. These progenitor cells have the ability to initiate prostate cancer in response to genetic changes.

uclahealth.org/increasedrisk

Antibiotic-Resistant Bacteria Hinders Treatment of Kidney Infections

UCLA researchers recommend development of new medications and new guidelines to address the increase in illnesses and deaths linked to medication-resistant bacteria that are making it more difficult to treat pyelonephritis, a common but severe kidney infection that can cause sepsis and death.

uclahealth.org/resistantkidneyinfection

Drug Shows Promise for Treating Alcoholism

UCLA researchers have found that an anti-inflammatory drug primarily used in Japan to treat asthma could help people overcome alcoholism.

uclahealth.org/treatingalcoholism

New Tuberculosis Therapy

Taking a new approach toward tuberculosis therapy, a UCLA-led research team has devised a potential drug regimen that could cut the treatment time by up to 75 percent, while simultaneously reducing the risk that patients could develop drug-resistant TB.

uclahealth.org/tbtherapy



Prostate Cancer

Immunotherapy Treatment Can Increase Survival for Some Patients with Prostate Cancer

Sipuleucel-T, the first therapeutic cancer vaccine to receive approval from the U.S. Food and Drug Administration, remains an important therapeutic option for patients with prostate cancer who have hormone-refractory metastatic disease and minimal or no symptoms, according to a UCLA urologist who participated in the clinical research leading to the drug's approval. The drug is among a broad class of cellular agents referred to as immunotherapies, which stimulate the patient's immune system to respond against the cancer.

"Immunotherapy has become the hottest area of oncology," says Allan Pantuck, MD, professor of urology. "The approval of sipuleucel-T — a personalized treatment that harnesses the patient's immune cells to identify and target prostate-cancer cells — stimulated the further development of this field by showing its feasibility and effectiveness as a cancer treatment."

The drug received FDA approval in 2010 on the basis of its survival benefit for men with metastatic prostate cancer, with minimal side effects. UCLA urologists were collaborators on the clinical trials that led to the drug's approval, and they have been treating patients with the drug since 2003. "This is not a cure, but it does seem to slow the progression of the cancer, and patients who take it live longer than those who don't," Dr. Pantuck says. He notes that the survival benefit averages about five months, though some patients can gain as much as a year from the treatment.

The drug is for patients with castrate-resistant metastatic prostate cancer who are either asymptomatic or minimally symptomatic. "The ideal candidates have asymptomatic small-volume disease with low PSAs, although we have given it to patients who are refractory to multiple treatments," Dr. Pantuck says. "The tolerability makes it easy to integrate into a treatment plan. We consider sipuleucel-T to be an important piece in the patient's overall treatment strategy that may involve many different types of therapy."

Sipuleucel-T is given to patients in three intravenous infusions administered in

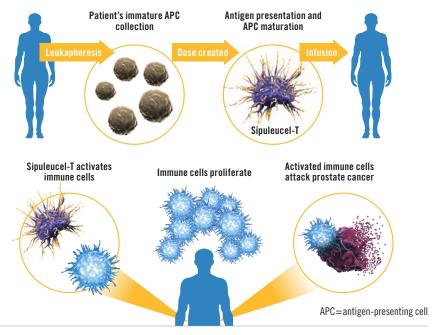
two-week intervals. Patients' immune cells are collected through a blood-drawing procedure called leukapheresis; then their cells are sent to a manufacturing facility, where they are grown in the presence of a protein that stimulates the immune cells to recognize prostate cancer. Several days after the cell-collection procedure, the patient receives a dose of sipuleucel-T. "This is a finite treatment that is given with three infusions over four weeks," Dr. Pantuck says. "The benefit of an immune treatment is that although it is given for only one month, like other types of vaccines to prevent infections, its effect on the immune system can be durable and long-lasting."

UCLA urology researchers and clinicians have been pioneers in using immunotherapy to treat urologic cancers since the mid-1970s, and they continue to be at the forefront of developing new immunotherapies. Laboratory research by Dr. Pantuck and colleagues has led to the development of GM-CAIX, a kidney-cancer vaccine currently in a Phase I/II clinical trial. "Immunotherapy appears to be a highly promising way to go for many cancers," Dr. Pantuck says. "It gives us a specific, individualized treatment that can recognize cancer, with fewer side effects than traditional chemotherapies."

"Immunotherapy has become the hottest area of oncology. The approval of sipuleucel-T ... stimulated the further development of this field by showing its feasibility and effectiveness as a cancer treatment."

Immature antigen presenting cells (APCs) are collected by leukapheresis and then matured by cell culture for three days in the presence of a fusion protein that includes prostatic acid phosphatase (PAP) to create a dose of sipuleucel-T. When the APCs are reinfused to the patient intravenously, they activate other immune cells to proliferate and attack prostate cancer cells expressing PAP.

Illustration: Dendreon Pharmaceuticals Inc.



Urologic Cancer

COVER STORY

New Chemo Vector Offers Option for Patients with Difficult to Treat Urologic Cancer

STORY HIGHLIGHTS

A new approach to treating upper-tract urothelial cancer has the potential to improve the delivery of chemotherapy drugs and to reduce the number of patients who lose a kidney as part of their treatment.

The approach delivers topical chemotherapy using a vector that is liquid at room temperature but becomes a gel at body temperature, solidifying in the renal pelvis and ureter to increase exposure time.

(continued from cover)

into the "sink" — the renal pelvis, ureter and bladder. For patients with upper-tract urothelial cancer — cancer that resides in the renal pelvis and ureter — recurrence is common after endoscopic surgery, and topical chemotherapy isn't an option because the ureters drain the liquid chemo into the bladder almost immediately, preventing any meaningful contact between the chemo and the tumor.

"The ureters are tubes that we can access only from the bottom, and when you squirt fluid up into the ureter, it just drains right out," explains Nicholas Donin, MD, urologic-oncology fellow in the UCLA Department of Urology. "We haven't had a way to keep the medicine up there.

"For patients with low-grade tumors that do not appear amenable to complete endoscopic treatment, this technology has the potential to save their kidney from having to be removed."

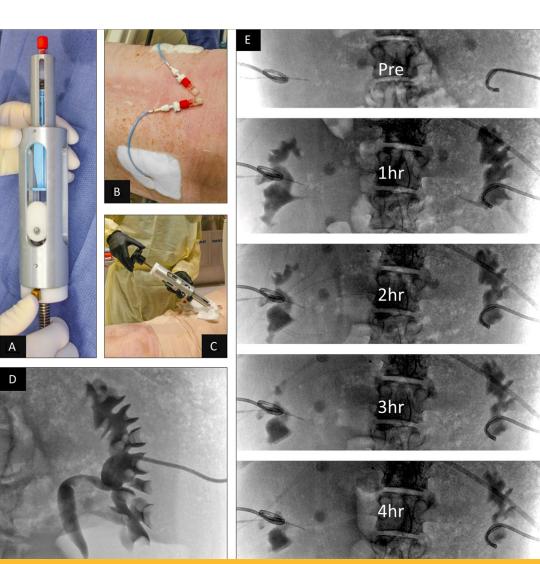
As a result, we haven't been able to treat these tumors with topical chemotherapy, even though we know that in the bladder, these drugs are effective." Although some patients with low-risk disease and favorable characteristics can be effectively treated endoscopically, he notes, most require radical nephroureterectomy — surgical removal of the kidney and ureter.

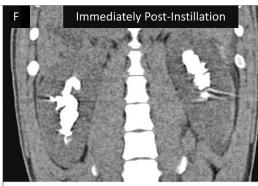
Dr. Donin is part of a UCLA urology team headed by Karim Chamie, MD, that has conducted a series of studies of a new approach to delivering topical chemotherapy to these tumors using a vector that is liquid at room temperature but becomes a gel at body temperature. A mixture of the liquid gel and chemotherapy drugs is injected into the renal pelvis and ureter, where it solidifies and takes on the shape of the cavity, enabling the course of chemotherapy exposure to last several hours rather than seconds to minutes.

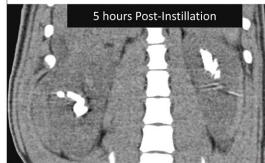
The UCLA team recently completed a threephase preclinical study evaluating the safety and technical feasibility of instilling the chemotherapy-impregnated gel in the upper urinary tract of a live-animal model. Among the findings, published in the journal *Urology*: The gel remained within the renal pelvis and



Photo: Getty Images









collecting system of the kidney for four-to-six hours. This prolonged contact time between the chemotherapy and the tumor was found to be safe, with minimal systemic absorption of the chemotherapy. The researchers found no evidence of any urinary-tract obstruction from the gel after it was delivered to the upper urinary tract, and no evidence of renal dysfunction, sepsis or bone-marrow suppression. Any histological changes in the kidneys, ureters and bladder were mild and appeared to be transient.

"For patients with low-grade tumors that do not appear amenable to complete endoscopic treatment, this technology has the potential to save their kidney from having to be removed," Dr. Donin says. "That is important because we know that losing a kidney increases the risk for cardiovascular events and death. There are also a fair number of patients who have only one kidney, and if their kidney is removed and they have to go on dialysis, that has significant

implications, particularly for the older patients who tend to be most affected by this disease."

UCLA is now part of a multicenter trial of the agent in humans starting this year. If OLYMPUS (Optimized DeLivery of Mitomycin for Primary UTUC Study) yields encouraging findings, the agent could ultimately gain approval from the U.S. Food and Drug Administration. In addition, the UCLA team is evaluating the potential use of the technology in conjunction with topical immunotherapy, which has been the standard of care for urothelial carcinoma of the bladder for approximately 30 years. "UCLA was critical in the early investigations of topical immunotherapy for the bladder," Dr. Donin says. "Now we are trying to couple this delivery mechanism with new topical immunotherapies."

- **A:** The specially engineered injection device used to instill the gel vector into patients.
- B: Injection tubes in animal model.
- **C:** Instillation of the gel vector into animal model.
- D: Image of animal-model-kidney anatomy.
- **E:** Timecourse X-ray images of gel dissolving over time in the kidney.
- **F**: CT scan images of gel within the kidney immediately following instillation and five hours later.
- **G**: Presence of gel within a kidney following instillation.

Images: Courtesy of Dr. Nicholas Donin

Men's Health

STORY HIGHLIGHTS

The Men's Clinic at UCLA offers a comprehensive and multidisciplinary approach to address a variety of male health issues.

The clinic aims to bring men into the healthcare system at an earlier age to encourage them to take steps to stay active and to prevent the illnesses that commonly afflict men as they age.

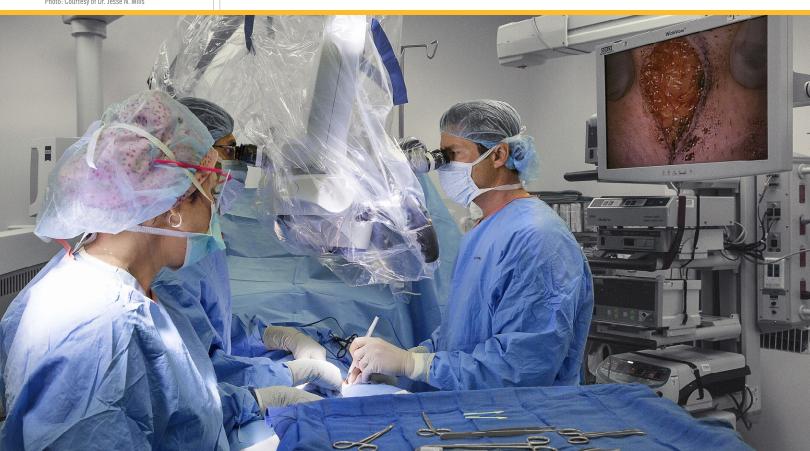
Photo: Courtesy of Dr. Jesse N. Mills

UCLA Clinic Takes Holistic Approach to Men's Health

The Men's Clinic at UCLA opened in 2015 in Santa Monica as a comprehensive, multidisciplinary health-and-wellness center. The clinic's physicians treat male sexual dysfunction and male infertility, with expertise in microsurgical vasectomy reversal, penile implant and prosthetic surgery, microsurgical testicular sperm extraction, male hormone-replacement therapy and sexual function after spinal-cord injury. In addition, the clinic collaborates with physicians in other specialties to meet men's holistic health needs. UCLA urologist Jesse N. Mills, MD, is the clinic's director.

How is the Men's Clinic at UCLA different from other men's-health clinics?

We are a comprehensive center that treats not just one disease state, but multiple aspects of male health under one roof. While many clinics emphasize testosterone therapy, we incorporate diet and lifestyle modification along with appropriate therapy to improve sexual health — potentially including testosterone replacement, medical and surgical therapies for erectile dysfunction and treatment for infertility. More broadly, our goal is to reach men who are



motivated to do everything they can to maintain or improve their health. We hope to bring men into the healthcare system at an earlier age so they can take the steps that will keep them active and help prevent the illnesses that commonly afflict men as they age. We want to help identify potential risks such as high blood pressure, high cholesterol, depression, erectile dysfunction, obesity and risky personal behaviors.

In that regard, is collaboration with other specialists central to your vision?

Absolutely. It used to be that there was the country doctor who took care of all of a patient's needs, but medicine is so much more complex now. As a urologist and a microsurgeon, my knowledge of cardiology is limited to what I learned in medical school. When I identify problems outside of my expertise, I need to be able to direct my patient to the best possible care. We see this interdisciplinary approach taking off in diabetes, in cancer care and in women's health, and it makes sense for men to also have a central place where they can meet all of their general-health needs. In our first year, we developed collaborative relationships with UCLA sports-medicine physicians and addiction-medicine specialists, for example, and we are pursuing closer ties with other disciplines to which our patients often are referred, such as cardiology, psychiatry and East-West medicine.

Why does it make sense to have urology as the cornerstone for this broader focus?

It comes down to Sutton's law, which is the classic story of Willie Sutton who, when asked why he robbed banks, said because that's where the money is. Sexual difficulties and urinary difficulties are what initially drive many men to the doctor's office, and so the urologist has the opportunity to steward them through the medical landscape. If I'm seeing a man in his 20s or 30s for fertility issues, I'm also thinking down the road about his risk factors for other conditions and how we can intervene to reduce them. If I'm seeing a 40-year-old man who is finished having kids and wants to schedule a vasectomy, and I see that he is overweight, I will discuss what he could do to improve his life over the next 10 years to make sure he doesn't develop heart disease, diabetes or other complications of obesity. In either case, the man is now

enfranchised into the medical system, and if he has issues or just needs a routine screening, he's more likely to return.

Why do men tend to be less proactive than women about their health?

There are two reasons. One is cultural. Men have been taught to "play through pain," which often translates to not seeking the care they need. That's had the unfortunate effect of marginalizing efforts to address men's overall health in a holistic way. It's amazing how many men will ignore even severe cardiovascular warnings. The second issue is that men between the ages of 18 and 50 are less likely than women to routinely see a doctor. Women generally see an internist or a gynecologist every year, and so they are regularly screened for hypertension, heart disease and cholesterol, as well as fertility health. Many men don't have that regular contact, and so they miss out when it comes to pointing out warning signs as well as on counseling to optimize their health.

What do you wish more physicians knew about male erectile dysfunction?

The first thing is that erectile dysfunction can often be a sign of other health concerns, such as significant cardiovascular problems, so a doctor who is just giving a prescription for an oral medication and not performing a full risk assessment is doing a disservice to the patient. And when it comes to treating the erectile dysfunction, there are lots of very good options that go well beyond the oral medication. Too many physicians and patients give up if the pills don't work, but those of us who are specialists in sexual medicine can offer more advanced therapies that can have a major impact on quality of life.



For more information about the Men's Clinic at UCLA, go to: urology.ucla.edu/mens-clinic







Jesse N. Mills, MD



A microbiology scientist examining bacterial growth isolated from a patient with a urinary-tract infection (UTI).

Photo: Getty Images

STORY HIGHLIGHTS

A broader approach to addressing recurrent UTIs involves more accurate diagnosis and treatment, closer attention to other risk factors and greater emphasis on patient education and prevention.

It is essential to educate women who have been confirmed to have recurrent bacterial UTI to recognize specific triggers.

Comprehensive Approach Needed to Address Recurrent UTIs

Addressing the problem of recurrent urinary tract infections (UTIs) among women requires a comprehensive approach that includes more accurate and timely diagnosis, improved use of antibiotics, closer attention to other treatable conditions and risk factors, and a greater emphasis on patient education and prevention.

There are an estimated 150-million UTI occurrences each year in the United States, resulting in more than 7-million physician visits, 1-million hospital admissions and \$6 billion in healthcare expenditures, notes Ja-Hong Kim, MD, associate professor in the UCLA Division of Pelvic Medicine and Reconstructive Surgery. One-third of women will develop a UTI by the age of 24, and roughly half of these women will have at least one recurrence within a year. Dr. Kim points out that the recurrent UTI population tends to fall

into two distinct categories: young, otherwise healthy women whose infections often are related to times of sexual intercourse; and a more complex population of women with a pre-existing urinary tract anomaly or who are elderly or immuno-compromised. "This complex group may need to be started on antibiotics earlier, because the stakes are higher. You don't want to miss any infections that could progress to kidney involvement," Dr. Kim says.

She notes that the problem of antimicrobial resistance is significant, with microbes evolving faster than the development of new drugs to treat them. "Some physicians are not following the practice guidelines for antimicrobial treatment of UTIs, and many women are being treated inappropriately without confirmatory cultures. Furthermore, inappropriate antibiotics that have potential for collateral damage are being

Women's Health

prescribed," Dr. Kim says. "The symptoms such as frequency, urgency and burning can coexist with other noninfectious bladder issues such as overactive bladder and interstitial cystitis, and patients who are reflexively being prescribed antibiotics may not have a bacterial infection at all."

Dr. Kim has developed a protocol for treating women with recurrent UTIs that begins with a thorough history and physician exam, as well as review of all past urine cultures to confirm that the patient does in fact have a UTI caused by bacteria and not something else. "You also need to assess for atypical organisms such as mycoplasma and ureaplasma, as well as viral and fungal causes," Dr. Kim says. "These do not get detected in a traditional urine culture, and they require a different type of antimicrobial treatment than what is given for a typical bacterial UTI."

For patients who have been confirmed to have recurrent bacterial UTI, Dr. Kim focuses on prevention through education, optimization of bladder/vaginal health and rebuilding healthy gut flora. She counsels patients to recognize triggers, including intercourse, frequent and uncontrolled bowel movements, and diet. If it is determined that the UTIs are related to intercourse, patients are instructed to take a low-dose antibiotic immediately after the encounter. Hydration also is important. "As long as one drinks plenty of fluids to make enough urine that completely empties when voiding, the bladder will flush out the offending organisms," Dr. Kim says.

Other prevention strategies include probiotics to restore the bowel flora, which can be affected by multiple courses of antibiotics. Vitamin C is recommended to boost the immune system, and cranberry tablets can be helpful in conjunction with other strategies, Dr. Kim says. She notes that cranberry tablets alone will not treat or prevent recurrent UTIs, based on recent studies. Some patients are encouraged to take supplements of D-Mannose, which can help to clear out the bacteria when there are early signs of a UTI. Dr. Kim also talks with her patients about perineal hygiene — a common contributor to recurrent UTIs among elderly and morbidly obese patients.

"Once you go through all of the prevention strategies, most patients will improve and see a drastic reduction in the number of UTIs," Dr. Kim says. For those who don't, and who have been found to have three or more culture-proven UTI episodes in a year, second-level measures include prescribing a methenamine — a powerful way to acidify urine to prevent bacterial growth. An office-based cystoscopy also is indicated for many of these patients. For some women, particularly older patients with complex UTIs, the bladder may be filled with pus, which needs to be drained. Dr. Kim describes this approach as being akin to a "power wash" of the bladder.

Some patients need to be broken of their habit of calling in for an antibiotic every time they experience symptoms of an infection. "When the patient is given antibiotics without a confirmatory culture, we are treating blindly and can erroneously prescribe inappropriate antibiotics," Dr. Kim says. For patients who are motivated to hold off on antibiotics until testing is done, Dr. Kim typically prescribes phenazopyridine and ibuprofen for symptom relief. "The real solution is giving the right antibiotic at the right time," Dr. Kim says. "Currently, I am collaborating on research to develop a rapid diagnostic assay that will allow accurate culture results in three hours, which is much quicker than the traditional 48-hour cultures."

Dr. Kim recommends that physicians whose patients are having three or more UTIs per year despite taking appropriate preventative measures refer their patients to a urologic expert. "Recurrent UTIs can have a significantly negative impact on quality life," she says. "If a woman is running to the bathroom every 15-to-30 minutes due to pain and urgency, she can't focus on herself, her work or her family. From a more global perspective, recurrent UTIs can be a dangerous source for propagating inappropriate antibiotic use that can have immeasurable impact on society through antibiotic resistance. We have to do everything we can to address this problem."



When evaluating for recurrent UTI, it is important to assess for atypical organisms such as mycoplasma (shown) and ureaplasma, as well as viral and fungal causes.

Photo: ScienceSource

There are an estimated 150-million UTI occurrences each year in the United States, resulting in more than 7-million physician visits, 1-million hospital admissions and \$6 billion in healthcare expenditures.



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U.S. News & World Report's Best Hospital Survey ranks UCLA No. 1 in Los Angeles, No. 1 in California and No. 5 in the nation.

Save the Date

UCLA Radiation Oncology Workshop: Integration of State-of-the-Art Innovations into Clinical Radiation Oncology Practice

June 2 - June 3, 2017

Neuroscience Research Building (NRB) Auditorium, UCLA Campus, Los Angeles, California



Recent advances have increased the repertoire of tools for radiation oncologists to maximize tumor control and minimize toxicity. This course will review state-of-the-art radiation-treatment strategies and provide a how-to approach to integrating new treatment modalities into a community radiation oncology practice, with the aim of helping practitioners to translate these advances into improved patient outcomes.



To enroll online, click on the event at: cme.ucla.edu/courses

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Physicians Update

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