Sister Act
Twin Receives the Ultimate Gift

For Liliana Quintanar, turning 18 brought an opportunity few other teens could fathom: the chance to donate a life-saving kidney to her identical twin sister, Analia.

In January, Liliana followed through on a vow she had made when Analia had been forced to go back on her daily 10-hour dialysis regimen at age 15, after her immune system rejected the kidney donated by the girls’ mother. Through UCLA Medical Center’s Pediatric Kidney Transplant program, Liliana gave her identical twin “the gift of life.”

Because of the unusual situation involving identical twins, the transplant—performed by H. Albin Gritsch, MD, associate professor in the Department of Urology, after the kidney was removed from Liliana laparoscopically by Dr Peter Schulam, head of the Division of Endourology and Minimally Invasive Surgery—leaves Analia with a healthy kidney that is almost certain to last her the rest of her life, with no need to endure the side effects of daily immunosuppressant drugs, as is required of recipients from non-identical twins.

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Patients with early-stage, localized prostate cancer are now able to choose from a multitude of treatment options, each with its own pros and cons on issues of efficacy and in quality of life impact. Given the individual nature of the treatment decision — research has not established that one therapy is best for everyone — a comprehensive program such as the UCLA Department of Urology's has many advantages.

“Our belief is that it is very important to tailor treatment to the patient’s tumor, age, expectations, personality and lifestyle,” says Robert Reiter, MD, associate professor of urology and co-director of the Prostate Cancer Program. Besides being the only program in the region to offer all existing treatments, the department monitors the results of each in an effort to provide better clarity for future decisions, conducts research leading to new therapies, and makes experimental treatments available to high-risk patients through clinical trials.

UCLA’s Prostate Cancer Program offers:

**Nerve-Sparing Radical Prostatectomy.** In the hands of experienced surgeons, the nerve-sparing radical prostatectomy — also called “open surgery” by comparison to the laparoscopic procedure — removes the cancer and preserves potency in the majority of men, with 80-90 percent of patients under the age of 60 regaining their sexual function. UCLA urologists have performed thousands of nerve-sparing radical prostatectomies over more than 15 years, with success rates that are among the nation’s highest. “The advantages of choosing this approach include a long track record with extremely good success rates,” says Dr Reiter, who does both radical and laparoscopic prostatectomies, as well as brachytherapy. Recovery time for the procedure is more rapid than in the past — hospitalization has been reduced to two days, with catheterization averaging seven days and patients returning to regular activities in as little as 2-4 weeks. The risk of urinary stress incontinence after one year is 5-10 percent.

**Nerve-Sparing Laparoscopic and Robotic Prostatectomy.** The laparoscopic approach to removal of the prostate is attractive to many patients because it is minimally invasive — involving five separate, small incisions with miniature instruments and magnification that affords the surgeons better visibility of some structures. There is less blood loss, which might result in less pain and shorter recovery times, particularly for older men, though that has yet to be proven. Indeed, as a newer approach — done at UCLA by Dr Peter Schulam together with Dr Reiter for more than three years, the longest record in Southern California — it is too early to gauge the laparoscopic surgery’s long-term effects, though so far the results are encouraging. “We’re finding with increased experience that it seems to be a good cancer operation, continence appears to be equivalent to the open operation, and as our knowledge of the technique has improved we are able spare the nerves, although it’s too soon to say that potency is equivalent to the open procedure, and much depends on the surgeon’s skill,” says Dr Schulam, noting that one procedure might be best for a given individual.

**Brachytherapy.** For more than a decade, UCLA has offered a prostate cancer treatment known as brachytherapy, in which a urologist, working in collaboration with a radiation oncologist and physicist, implants small radioactive pellets, or seeds, into the prostate under ultrasound guidance. The pellets then emit high doses of radia-

Plain film x-ray after radioactive seed placement into the prostate
Brachytherapy places radioactive “seeds” – some urinary frequency or slow urination issues that can be treated medically, and a risk of impotence in older men that appears to be lower than surgery. Most patients can return to their regular activities within a few days.”

Intensity-Modulated Radiation Therapy (IMRT). The new state of the art in external-beam radiation therapy, IMRT is an ultra-precision oriented treatment in which the radiation beam can be configured to conform to the shape of the prostate, enabling high doses to be delivered while reducing damage to the surrounding normal tissues. “By doing precision-oriented radiotherapy like IMRT, we believe we will be able to drive PSA down lower than in the past, which we hope will translate into a survival advantage,” says Dr Steve Lee, UCLA radiation oncologist, though he points out that the technology is too new for there to be long-term results. IMRT is a complicated procedure requiring expertise from not only radiation oncologists but also qualified physicists and technologists. Depending on the patient’s initial disease presentation, at UCLA the high-precision technology is generally offered as a “boost” to traditional external-beam radiation therapy, to ensure that the treatment field still covers possible tumor extension adequately. The entire course involves about eight weeks of time, every weekday, about 10 minutes per day. “Surgery is very useful when we know for sure that the tumor is within the prostate gland, but when there is significant doubt about whether it has escaped the prostate, radiation can cover the peri-prostatic tissue,” notes Dr Lee.

Cryotherapy. Freezing the prostate cells as a strategy for killing the tumor was first used in the 1960s, but abandoned due to unacceptable complications. It was revived more than a decade ago with the advent of transrectal ultrasound, allowing the urologist to see the prostate while inserting needles containing liquid nitrogen into the prostate gland to create ice balls. Within the last several years, a third-generation cryotherapy technique has reduced the complications by using argon gas delivered through very small needles. Once the argon freezes the prostate, helium gas can be inserted to make it thaw. “It’s a much quicker process than when we used nitrogen,” says Dr Ken-ryu Han, a urologic oncology fellow working with Dr Arie Beldegrun, who leads UCLA’s cryotherapy program, “and because the needles through which the argon and helium are delivered are so much smaller, the risk of complications appears to be lower. It’s too soon to be able to say whether or not this type of cryotherapy is here to stay, but it is a good option for certain patients.” Candidates include patients 70 years and older or men who are otherwise poor candidates for radical prostatectomy, and those who have a recurrence after initially being treated with radiation—after which radical prostatectomy is rarely an option. Though it appears to have the advantages of less blood loss and quicker recovery than radical prostatectomy, cryosurgery results in impotence for nearly every patient, since the nerves vital to erection are frozen.

Experimental Therapies.

Although improvements in treatment for localized prostate cancer have resulted in excellent survival rates overall, men with certain types of prostate tumors are considered to be at particularly high risk for experiencing recurrence. “Radiation or surgery alone might cure only 30–40 percent of these men, so we know that better treatments are needed,” says Dr Reiter. UCLA’s Department of Urology is a leader in developing new therapies through the Prostate Cancer Research Program—recently designated a Specialized Program of Research Excellence by the National Cancer Institute—and in offering experimental therapies to high-risk patients through clinical trials. Among the exciting trials currently under way is one that tests the efficacy of the immunosuppressant drug CCI-779, which was found in the UCLA laboratory of Dr Charles Sawyer to slow the growth of certain tumors.

While clinical trials follow strict protocols and are closely monitored, two large databases maintained by the Department of Urology are also keeping tabs on survival and quality of life outcomes for prostate cancer patients treated non-experimentally at UCLA. “There is still not enough evidence for anyone to be able to claim that one treatment is superior to another,” says Dr Reiter. “Each treatment has unique benefits and disadvantages. We might think certain approaches are superior for certain patients, but it’s important to be able to prove it.”
“This was a family effort,” says Dr. Gritsch. “It’s very touching that Liliana knew for so long that this operation was coming, and that as soon as she turned 18 she went forward to help her sister, who will now be able to lead a normal life.”

“I’m so thankful for Liliana,” says Analia, “because if it wasn’t for her, I don’t know what I would have done.”

Analia was born with renal dysplasia—for unknown reasons, her kidneys would not develop. Her doctors told her parents that if she didn’t receive a donated kidney within two weeks of birth, she would need to go on dialysis to stay alive. At the same time, there was some good news—Analia’s identical twin sister, Liliana, was born perfectly healthy.

Because there was no compatible donor kidney available for Analia during her infancy, her parents had to connect her every night to a dialysis machine, which exchanged fluids in her abdominal cavity for 10 hours as she slept. That lasted until Analia turned 5, by which time she was big enough to receive her mother’s kidney. The transplant enabled Analia to live her life free of dialysis for 10 years. At 15, when that kidney failed, she returned to the nightly routine.

Beyond the inconvenience and discomfort, children with kidney failure experience a number of other adverse consequences that affect their quality of life, Dr. Gritsch notes. Among other things, their growth is often stunted, their bones can be weak and their blood counts tend to be low, leading them to feel weak and easily tired. Their diet is restricted and they are at greater risk for developing infection from catheters entering their bodies.

Liliana had watched her sister suffer. “Analia has been in and out of hospitals since the day she was born,” she says. “I decided to donate my kidney to my sister when I was 16 because I was so tired of seeing her go through so much pain. I know it will give her the opportunity to live a better life, which will make me and my family really happy.”

Dr. Gritsch explains that the transplant team had required Liliana to wait until she was an adult for two reasons: to make sure she was not going to develop any kidney problems, and because ethically, it was deemed to be appropriate for Liliana to make such an important decision as an adult. Liliana’s prognosis following the transplant is excellent. “Donating a kidney does not increase one’s risk of developing kidney disease,” Dr. Gritsch notes. Moreover, Dr. Schulam performed the procedure removing Liliana’s kidney laparoscopically—the very small incision resulting in less scarring and a much more rapid recovery.

As for Analia, the unusual case of receiving an organ from someone who shares her genetic makeup leaves her with a kidney that will not be recognized by her body as foreign, rendering the immunosuppressant drugs she took every day after receiving her mother’s kidney unnecessary. Side effects from daily immunosuppressant medications can include high blood pressure, nausea, a tendency toward infections, weakened bones that can lead to osteoporosis at a young age, increased risk of cataracts, and cosmetic effects that can include excessive hair loss or growth and severe acne.

Many young sufferers of kidney failure are not as fortunate as Analia, Dr. Gritsch notes. More than 200,000 people in the United States are currently on dialysis, including nearly 10,000 children. More than 40,000 people are on the waiting list to receive a donated kidney. Each year, approximately 300 kidney transplants are done in both adults and children, one-third of them from living donors. UCLA’s Pediatric Kidney Transplant program, one of the most active and successful programs of its kind in the United States, has given transplants to more than 500 children since it was established in 1980.

While receiving a kidney from an identical twin represents the ideal situation, all that is required for a donor match is the same blood type. Approximately one in five living-donor kidney transplants at UCLA is from an unrelated individual. “It’s no longer a miracle that someone is a match to donate a kidney,” Dr. Gritsch says. For people who choose to designate that their kidneys be donated after death, a national system, administered by the United Network for Organ Sharing (UNOS), determines the best match for cadaveric kidneys among patients on the waiting list.

“Not everyone has an identical twin, and there are lots of people out there who would benefit from a kidney,” notes Dr. Gritsch. “This was a rare case. The majority of people with kidney failure are waiting for the generosity of families who are willing to allow organ donation after death.”

For information on organ donation, call (800) 786-4077.

Clockwise from left: H. Albin Gritsch, MD (surgeon); Robert Ettenger, MD (nephrologist); Jennifer Marik, RN (transplant coordinator); Liliana Quintanar (donor); Analia Quintanar (recipient)
half of advanced bladder cancer patients experiencing recurrences. And at best, aggressive chemotherapy treatment only slows tumor progression in patients whose cancer has moved outside the bladder.

But the known risk of smoking, the long latency period of the disease (close to 20 years following initial exposure), the development of intermediate “biomarkers” that predict later cancer and the accessibility of the bladder for non-invasive urine sampling also make bladder cancer an ideal target for studying the disease and developing new treatment and prevention strategies. That’s the main focus of a five-year, $7 million UCLA bladder cancer program funded by the National Cancer Institute (NCI)—a multidisciplinary effort based in the Department of Urology.

As with the department’s successful programs in prostate and kidney cancer, the bladder cancer program will include basic research studies and clinical trials, along with translational efforts to continue converting knowledge gained in the laboratory to advances in early diagnosis and patient care. “It is very important to have all three components,” says Arie Beldegrun, MD, professor of urology, chief of urologic oncology and principal investigator of the NCI-funded grant program.

The basic science aspect is built around work done by Dr Beldegrun and Dr David Seligson, a pathologist, in establishing a database for approximately 600 cases of patients treated for bladder cancer at UCLA. The history of these patients, beginning from the time of diagnosis, is correlated with the genetic profile of their tumors, using tissue microarray technology—the high-throughput method of rapidly screening tissues for particular genetic characteristics. “This is a very powerful program that enables us to come up with a signature for every patient’s tumor,” Dr Beldegrun explains. By doing so, the researchers can not only improve prognosis for bladder cancer patients, but can identify and develop targeted therapies for specific populations of patients, and help clinicians choose the best course of treatment.

The first major clinical trial proposed by the program aims to develop an effective chemoprevention strategy to reduce the risk of bladder cancer recurrence. The study calls for more than 300 former smokers with a history of superficial bladder cancer to be given daily oral doses of Tarceva (erlotinib), green tea extract or a placebo, in an effort to assess the impact of the agents on the risk of tumor recurrence. Dr Robert Figlin, professor of hematology/oncology and urology, and Dr Allan Pantuck, assistant professor of urology, lead the clinical effort.

“There are no oral agents currently approved to prevent superficial bladder cancer or its recurrence,” notes Ronald Lieberman, MD, program director for NCI’s Division of Cancer Prevention. “From a clinical point of view, this is an important niche that needs to be addressed.”

Standard treatment for patients with this form of cancer is cystoscopy and surgery to remove the tumors, along with intravesical therapy, which consists of drugs placed into the bladder through a urethral catheter in an effort to minimize the risk of tumor recurrence and progression. Besides being at a high risk for recurrence, Dr Lieberman notes, these patients must be followed closely with visits to the urologist every 3-6 months for maintenance therapy.

Among other things, the clinical trial could provide new insight into the question of whether smoking cessation affects one’s risk of developing bladder cancer, says Nazy Zomorodian, RN, MSN, NP, CCRC, a urology nurse practitioner and director of the Clark Urological Center’s Clinical Trials Office. Ms Zomorodian notes that by following patients over a period of time for evidence of pre-malignant lesions, the study could also provide information about tumor biomarkers, which could lead to new strategies for early detection, as well as suggesting other treatment approaches.

Dr Zuo-Feng Zhang, professor of public health, and Dr Jian Yu Rao, associate professor of pathology and laboratory medicine, aim to develop such biomarkers.

Members of the bladder cancer chemoprevention clinical trial team, from left: Elizabeth Tran, Arie Beldegrun, MD, Robert Figlin, MD, Allan Pantuck, MD, Nazy Zomorodian, MSN, Annette Tan

KUDOS:

Mark S. Litwin, MD, MPH

professor of urology and public health, received a $1.6 million, five-year grant from the National Institutes of Health for “Chronic Prostatitis Collaborative Clinical Research Network,” for a clinical trial center at UCLA, Harbor-UCLA Medical Center, and Martin Luther King-Drew Medical Center that will participate in collaborative, multi-site trials sponsored by the newly established, National Institute of Diabetes & Digestive & Kidney Diseases-sponsored Chronic Prostatitis Collaborative Research Network. The study will develop a clinically relevant definition of the urologic chronic pelvic pain syndrome, based on the clinical findings from these and other related clinical studies.

Sally Maliski, PhD, RN

assistant researcher, received a three-year, $340,920 New Investigator Award from the U.S. Department of Defense for “The Meaning of Incontinence and Impotence for Low Income African American and Latino Men with Prostate Cancer,” focusing on patients being treated for prostate cancer in a free state-funded program in California.

Larissa Rodríguez, MD

assistant professor of urology, received a five-year, $1.9 million grant from the Center for Scientific Review for “Autologous Adipose Derived Stem Cells for Treatment of Incontinence.” The grant supports Dr Rodríguez’s effort to develop an injectable combination of cells, factors, and matrix to promote the development of vascularized, long-lasting functional urethral musculature.
Promising Developments in Bladder Cancer Studies

Studies in the laboratory of Robert Reiter, MD, associate professor of urology at UCLA, show potential for improving bladder cancer diagnosis and treatment as well as for providing a better understanding of the molecular basis for the disease.

Dr Reiter and his colleagues have made several key discoveries related to the prostate stem cell antigen (PSCA) gene, which they identified in 1997. Among other things, they found that the gene is expressed at abnormally high levels in 80 percent of human prostate cancers, suggesting that it could be a useful tool for prostate cancer detection. The specificity of the PSCA protein also provides a target for antibodies to attack. With a biotechnology company, Dr Reiter’s group developed antibodies and demonstrated in a laboratory setting that they were effective in slowing the growth of prostate tumors. But in their studies of PSCA, Dr Reiter and colleagues have found something else: It is also expressed highly in many bladder cancers. As with prostate cancer, this suggests that PSCA could be a useful diagnostic marker, and it raises the possibility of antibody therapy.

The emergence of a new diagnostic test for bladder cancer in men would be particularly welcome given that the results of standard urine cytology tests can miss many low-grade or slow-growing cancers, and cystoscopy, while more accurate, is both expensive and invasive. But Dr Reiter, in collaboration with Dr Jian Yu Rao in UCLA’s Department of Pathology, recently completed a study in which they found that the presence of a PSCA-positive cell in urine samples can identify 80 percent of men with bladder cancer.

“Our initial research suggests that this is clearly superior to conventional cytology as a diagnostic tool, and there are very few false positives,” says Dr Reiter. His group now wants to pursue a larger, prospective study to determine whether PSCA could be a useful screening test for men with bladder cancer symptoms.

On the therapeutic side, Dr Reiter and colleagues have tested the same antibody used against PSCA in prostate cancer and have found that, in the laboratory setting, it is effective in slowing the growth of bladder cancer.
cancer tumors. “In the long term, our goal is to develop this as a therapy for bladder cancer as well,” Dr. Reiter says.

Elsewhere in Dr. Reiter’s lab, a team that includes Dr. Isla Garraway, a fifth-year resident, and Dr. Chau Tran, a postdoctoral fellow, is developing a mouse model for human bladder cancer. Unlike prostate, breast and other cancers that have multiple models for studying the disease in the laboratory, there is a scarcity of such tools for bladder cancer. “One of the reasons this cancer is understudied is that we have lacked good mouse models that mimic the disease in humans, giving us a platform for looking at the genetics of cancer formation and progression, determining targets for treatment, and testing new therapies,” Dr. Garraway explains.

The most commonly used current model involves a transgenic mouse—an animal whose genetic makeup can be changed so that it overexpresses a single cancer-causing gene. The drawback is that only one gene can be studied at a time. In addition, because of technical issues, current transgenic models study the effects of cancer genes turned on immediately at birth or before—but most cancers of the bladder and other organs are the result of mutations in adult cells. Drs. Garraway and Tran have worked with Dr. Reiter to develop a different type of model, in which the mouse expresses a receptor for a virus in its bladder, then the virus carrying cancer-causing genes is injected, potentially enabling the virus carrying cancer-causing genes to study another gene—a very expensive approach. Instead of having a transgenic mouse model to study one gene, then making another to study another gene—a very expensive process—we hope to use one model to study multiple cancer-causing genes simultaneously,” Dr. Garraway explains.

Moreover, the researchers have attached to the virus the gene responsible for luminescence in the firefly, which has allowed them to image the infected mice to determine non-invasively whether the genes are transferred effectively and, potentially, to watch the tumor development and progress in the bladder. The group intends to continue exploring different combinations of genes to learn more about how bladder tumor formation is caused.

Eric Jones was inspired by faculty mentors to pursue a career as an academic researcher. Since completing his residency in 2000, Dr. Jones has been doing exactly that, as he works toward his goal of developing a top-notch National Institutes of Health (NIH)-funded clinical research program in pediatric urology at Baylor College of Medicine.

In addition to seeing patients at Texas Children's Hospital, where he serves as urologic director of the multidisciplinary Spina Bifida Clinic, Dr. Jones is assistant professor of urology and a scholar in Baylor’s Clinical Scientist Training Program. He is particularly interested in developing new management strategies for neurogenic bladder dysfunction, a common problem among children with spina bifida in which the disturbance of neurological pathways regulating bladder function leaves them unable to void or hold urine appropriately. “This is more than just a quality of life problem; it’s a health issue,” Dr. Jones notes. “It can lead to kidney or bladder infections and, in the long term, kidney failure.”

As many as half of children born with spina bifida are unable to empty their bladder, causing them to store urine at high pressures and putting their kidneys at risk. These patients are typically treated with intermittent catheterization. But even then, at least 15 percent ultimately suffer upper urinary tract deterioration. Last August, Dr. Jones received funding from the NIH to develop a two-year pilot study of a new approach: the use of botulinum toxin—the same substance popularly used for ironing out wrinkles—to reversibly paralyze the urethral sphincter. “Our hypothesis is that if we can inactivate the urethral sphincter during the early course of these children’s lives, we will be able to both prevent those upper-tract changes and preserve the patients’ ability to hold urine when it comes time to trying to get them continent, which is usually when they reach the school-age years,” Dr. Jones explains. He hopes to begin recruiting patients for a clinical trial within the next several months.

At the same time, Dr. Jones is working with the hospital to establish a Voiding Dysfunction Center for children with non-neurogenic disorders. “As I began working here, I saw a great need to provide better care for kids with daytime wetting,” he says. “At age 7, probably 5-10 percent of kids have some degree of problem with this. It’s socially stigmatizing and still not very well understood.”

Dr. Jones’ interest in pediatric urology began during residency, when he worked with Dr. Bernard Churchill, director of UCLA’s Clark-Morrison Children’s Urological Center. Having learned about neurogenic bladder disorders under Dr. Churchill’s tutelage, Dr. Jones decided to take his expertise to Texas, doing a two-year pediatric urology fellowship at Baylor before joining the faculty.

“I was fortunate at UCLA to have excellent people to work with,” he says. “The research opportunities got me thinking about things scientifically and cultivated my interest in pursuing an academic career. The members of the faculty are all top caliber, and when you’re surrounded by such greatness, it compels you to be the best that you can be.”
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