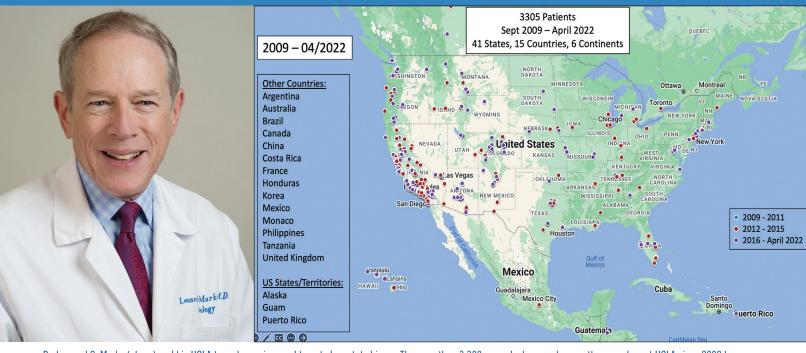




UCLA UROLOGY

UPDATE



Dr. Leonard S. Marks (above) and his UCLA team have pioneered targeted prostate biopsy. The more than 3,300 men who have undergone the procedure at UCLA since 2009 have come from 43 U.S. states and 14 countries covering six continents.

Innovations Transform Diagnosis and **Treatment of Prostate Cancer**

rostate cancer remains a leading threat to the health of older men — in the U.S., it is the second-commonest cause of cancer death in men and the most common malignancy diagnosed among males other than skin cancer. But in a little more than a decade, a remarkable transformation has occurred in how the disease is diagnosed and treated. At the heart of the dramatic change: a decline

in radical prostatectomy and radiation therapy — the traditional mainstays of prostate cancer treatment, which, while effective, are associated with significant sexual and urinary side effects. In their stead, more patients are being managed with so-called active surveillance — closely observing rather than treating cancers deemed low-risk — and focal therapy, which uses ablation techniques to destroy the cancer tissue while sparing the prostate, analogous to lumpectomy treatment for breast cancer.

Leonard S. Marks, MD, UCLA Urology professor and holder of the department's Jean B. deKernion Chair, sums up the progress this way: "This is not your father's prostate cancer."

Dr. Marks, who trained at UCLA, then spent time in private practice before joining the UCLA Urology faculty in 2009, has played an important role in those advances, in collaboration with a multidisciplinary team of colleagues from UCLA's departments of urology, radiology, pathology, and bioengineering.

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Prostate Cancer

For information on making a gift to UCLA Urology, please log on to http://giving.ucla.edu/urology or call (310) 206-4565.

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Dr. Marks (front row, center) with his team. Back row, I. to r.: Elizabeth U. Tran, BS (clinical research coordinator); Kyle Crisostomo, Sr., LVN (urology); Marlon Magat, BSN, RN, CNOR (charge nurse, Ambulatory Surgery Center); Anthony Sisk, DO (pathology); Rory Geoghegan, PhD (bioengineering); Jake Pensa, MD (bioengineering); Mark Topoozian, BS (student volunteer); Laura Guzman (certified surgical technician, Ambulatory Surgery Center); Samantha Gonzalez, MA (clinical research coordinator). Front row, I. to r.: Sean J. Lee, MPH, PA-C (urology); Dr. Marks; Merdie Delfin, MSN, NP (clinical research coordinator).

Their transformative efforts began in the area of diagnosis. The prostatespecific antigen (PSA) blood test has long served as the primary screening tool. In the past, when men's PSA was elevated, they typically underwent a biopsy in which, under the guidance of transrectal ultrasound imaging, samples of the prostate tissue were taken and then tested for cancer. But because

ultrasound doesn't clearly display the location of tumors in the prostate gland, these were blind samples, Dr. Marks notes.

"The problem was that for every patient in whom we found cancer, there were 3-4 who didn't have cancer and didn't need the biopsy," Dr. Marks says. "Moreover, that cancer you found was most commonly one that we now know didn't require treatment; it just needed to be observed through active surveillance." These tumors, carrying a Gleason score of 6 under the standard grading system for determining the cancer's aggressiveness, are considered to be very slow growing and unlikely to become life threatening, Dr. Marks notes.

The major shift in how prostate cancer is diagnosed can be traced to the use of magnetic resonance imaging (MRI). Whereas ultrasound shows the prostate but often doesn't reveal the location of the cancer, MRI shows the cancer in about 80% of

"When you know

exactly where to put the

biopsy needle, you have

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cases. When Dr. Marks joined the UCLA Urology faculty, MRI was just starting to be used in prostate cancer — mostly to determine how aggressive the tumor was before surgery. That began to change as Dr. Marks and his colleagues started using MRI prior to biopsy for patients with elevated PSA. With the

help of donor funds, UCLA Urology obtained one of the first machines capable of fusing MRI with ultrasound, allowing Dr. Marks and his team to view the MRI image while performing the ultrasound-guided biopsy, and thus take tissue samples from the lesions revealed by the MRI.

Recognizing the untapped potential in this image-fusion approach, Dr. Marks enlisted UCLA's bioengineering department as part of a multidisciplinary collaboration around prostate MRI. Over the next decade, the team (also

including urologists, radiologists, and pathologists) further developed the MRI/ultrasound fusion biopsy, showing in a study published in 2019 that it detected 33% more cancers than standard methods. Equally important, Dr. Marks notes, the method is far more likely to reveal the cancers that are more aggressive and require treatment, which show up as "hot spots" on the MRI and can be targeted in the biopsy procedure. "When you know exactly where to put the biopsy needle, you have a much better chance of getting answers about a tumor," Dr. Marks says.

The ability to identify the precise location of the cancerous tissue in the prostate also opened the door for a transformation in prostate cancer treatment. "If we can identify the location of tumors, biopsy them, and characterize them accurately, why not use energy to destroy them while leaving the rest of the prostate alone so as to minimize the side effects of treatment?" Dr. Marks says.

Focal therapy, or partial gland ablation, is patterned after the lumpectomy for breast cancer — but instead of surgical excision, it employs minimally invasive energy to destroy the cancer tissue, under ultrasound guidance and with the information derived from MRI. Dr. Marks' team at UCLA was among the first in the U.S. to initiate focal therapy, and has treated more than 200 patients over the last several years using two approaches: high-intensity focused ultrasound (HIFU), which heats the tissue; and cryotherapy, which freezes it.

Patients are candidates for focal therapy if they have intermediate-risk prostate cancer (Gleason score of 7) located in one area of the prostate, and have a prostate gland that is not too large. As with active surveillance, focal therapy patients

are followed closely after the procedure, receiving a follow-up biopsy six months later and another a year after that. Dr. Marks estimates the success rate after six months to be 75%-80% — and, for the remaining patients, the procedure can be repeated, or they can opt at any point for radical prostatectomy

or radiation therapy. "You don't burn any bridges behind you with focal therapy," Dr. Marks says, "and the side effects in terms of erectile dysfunction and incontinence are dramatically less."

More recently, a UCLA-backed startup company, Avenda Health, has begun incorporating information from thousands of biopsies recorded by the image-fusion device to develop a focal therapy system that uses artificial intelligence to further refine the approach, helping to identify appropriate treatment margins. Dr. Marks is a co-founder and chief medical officer for the company, which is headed by his long-time collaborator from the UCLA bioengineering department, Shyam Natarajan, PhD. In June, the product was granted breakthrough device designation by the FDA.

Dr. Marks' team has compiled a database with information on approximately 5,000 image-fusion biopsies, more than 1,000 patients on active surveillance, and more than 200 focal therapy patients.

"Prostate cancer diagnosis and treatment continues to evolve," he says. "When I started on the UCLA Urology faculty, my goal was to make diagnosis more accurate and treatment simpler. We are well on the way."

For more on targeted prostate biopsies, visit www.TargetedProstateBiopsy.com.

Collaboration With Engineers Proves Fruitful

The efforts of a team headed by UCLA Urology's Dr. Leonard S. Marks to transform prostate cancer diagnosis and treatment have been buoyed by the expertise of a group of UCLA engineers. In their own words, they describe their experience with the collaboration.



Rory Geoghegan

I have been working with Dr. Marks for the last eight years to develop focal laser ablation for treating prostate cancer. This is a truly multidisciplinary project with a team including urologists, pathologists, radiologists, and engineers. As an engineer

myself, it is exciting to work in an area that has a real tangible benefit for patients. My specific focus has been on developing sensors for providing real-time feedback during laser ablation. We have been able to take this all the way from a simple napkin sketch through preclinical testing and, recently, validation in a clinical trial. This has been a thoroughly fulfilling journey, as generally academic projects in engineering fail to translate to clinical use. Ultimately, we hope our technology will see widespread adoption and provide a much-needed solution for the many men struggling with prostate cancer.



Jake Pensa

I am a fourth-year bioengineering PhD student working as a part of Dr. Marks' research team. My work is focused on evaluating the ability of various imaging modalities for visualizing clinically significant prostate cancer, as well as determining why

certain cancers are invisible on imaging. The goal of this work is to improve the overall detection of prostate cancer as well as the affordability and accessibility of accurate prostate cancer diagnosis. In particular, we just concluded enrollment on a clinical trial to compare the diagnostic ability of a new form of ultrasound imaging known as Micro-ultrasound and multi-parametric MRI against ground-truth histology data. Overall, working as a part of Dr. Marks' group has afforded a unique and rewarding opportunity to be part of a multidisciplinary team with the common goal of improving patient care.



Shyam Natarajan

My work involves investigating image-guided interventions for prostate cancer, from better methods of imaging to new forms of therapy. One of the exciting active projects involves applying artificial intelligence to improving decision-making and outcomes in men

undergoing management and treatment for prostate cancer. Through a collaboration with Dr. Marks, we obtained an Academic-Industrial Partnership grant from the National Cancer Institute that has spawned a spinout company, Avenda Health, which is bringing this technology to market so it can benefit patients on a larger scale. By visualizing not only suspicious areas of tumor but also likely tumor extent, we are enabling better personalization and a new method of targeted therapy — focal laser ablation, which has the potential to offer treatment at the bedside while preserving quality of life. In clinical trials, we showed the ability to perform this form of therapy in a doctor's office under local anesthesia.



Alan Priester

Dr. Marks spearheaded an incredibly fruitful collaboration between engineering and urology, and we've been working together since 2012. Among our many innovative projects, we founded a program where 3D-printed, patient-specific slicing templates

were produced for radical prostatectomy cases. We examined each surgically removed prostate using a 3D-printed piece customized to their anatomy. That way, we could perform very precise comparisons between what the radiologist saw on MRI and what pathologists saw under a microscope. We found that MRI tends to underestimate the extent of tumors, which has important implications for targeted biopsy and therapy. We also created custom hardware and specialized software in order to perform the nation's first ultrasound-guided focal laser ablation of prostate cancer. Instead of removing or irradiating the entire prostate, we treated the tumor very precisely using a fiber-optic laser. That way, prostate cancer could be treated safely in an outpatient clinic, with no side effects and no hospitalization.

Christopher Filson, MD, MS



hrough his urologic oncology fellowship training at UCLA from 2013 to 2015, Dr. Christopher Filson became involved with the groundbreaking efforts of a multidisciplinary team headed by Dr. Leonard S. Marks, UCLA Urology professor, to improve the diagnosis of

prostate cancer through the use of magnetic resonance imaging (MRI) and MRI-ultrasound fusion biopsies (see this issue's cover story). And, through the mentorship of Dr. Mark S. Litwin, UCLA Urology professor and chair, Dr. Filson delved into population-level health policy issues, including how to ensure that important advances such as image-fusion biopsies are broadly adopted in community settings.

Today, as associate professor of urology at Emory University School of Medicine and co-director of the urology department's Health Services Research Core, Dr. Filson is making the most of that training. He's using the expertise he gained to further hone the MRI-ultrasound fusion prostate biopsy, as well as studying novel biomarkers for active surveillance approaches to managing low-risk prostate cancers. And he's conducting research aiming to bring the advances in these areas to all populations that could benefit from them, including those that have been traditionally underserved.

For the past four years, Dr. Filson has studied these issues with funding from a prestigious American Cancer Society career development award. "We're learning more about the advantages of using MRI to determine whether a patient needs to undergo a biopsy, which is an invasive procedure, after an abnormal PSA test," Dr. Filson says. "When findings of that MRI are concerning, the studies suggest that we may be able to more accurately identify higher-grade cancers with the MRI guidance than with ultrasound alone — and thus to better inform patients about what treatment approach might be best for them. Through that grant, we have also been able to highlight the disparities in who receives MRI for prostate cancer detection. Now we hope to move beyond that to determine actionable interventions that can prevent those disparities from being perpetuated."

Dr. Filson says his UCLA Urology fellowship — under the mentorship not only of Drs. Marks and Litwin, but also Drs. Arie Belldegrun, Allan Pantuck, and Robert Reiter — has been instrumental to his early research and clinical successes. "I'm so grateful to have been given the opportunity to train in one of the premier programs in the country for urologic oncology, and to have learned from the best-of-the-best through their stellar mentorship, as well as having opportunities to work alongside premier pathologists, radiation oncologists, medical oncologists, and others in multidisciplinary settings," he says. "I've carried that training with me to Emory, and it's been exciting to have the opportunity to pass along the knowledge and skills I gained at UCLA to the students and residents here."

HEALTHY AT EVERY AGE

Focal Therapy for Prostate Cancer

pproximately 175,000 men are diagnosed with prostate cancer each year in the United States. When the cancer has not spread outside the prostate gland, treatment with conventional surgery (radical prostatectomy) or radiation therapy is highly effective in curing patients of the cancer, but both are associated with significant side effects that can compromise quality of life. For this reason, and because many prostate cancers are slow-growing and unlikely to ever cause a problem for the patient, a growing number of men who are found to have low-risk prostate tumors choose active surveillance, in which the cancer is closely monitored and treated only if and when it becomes a threat. For patients with intermediate-risk cancers — not immediately life-threatening but considered too risky to follow in active surveillance — a minimally invasive treatment strategy has emerged, analogous to the lumpectomy for breast cancer treatment. This approach is known as focal therapy.

Focal therapy destroys the tumor while sparing the healthy prostate tissue, significantly reducing side effects associated with conventional treatments, such as incontinence and erectile dysfunction. This has become feasible in recent years because of the growing use of sophisticated magnetic resonance imaging (MRI) in prostate cancer diagnosis, which shows with precision where the tumor is located in the prostate gland, enabling physicians to place a biopsy needle specifically into that spot and characterize with greater accuracy how aggressive the tumor is likely to be. Two focal therapy approaches have been approved for use by the U.S. Food and Drug Administration: high-intensity focused ultrasound (HIFU), which delivers powerful ultrasonic energy to destroy the tumor; and cryotherapy, which destroys the tumor by delivering energy that freezes it.

Patients are considered candidates for focal therapy if they have intermediate-risk prostate cancer (a Gleason score of 7) in which the tumor is confined to one identifiable part of the prostate, and the prostate gland is not unusually large. UCLA has treated more than 200 patients with focal therapy since 2019. Because the therapy is still considered investigational, every man who receives focal therapy at UCLA undergoes a follow-up MRI-guided biopsy six months after the treatment, and then another one a year after that.

For more information, visit www.uclaurology.com. To make an appointment, call (310) 794-7700.



Letter from the Chair



ome of the most important advances in health care result from collaborations between biomedical researchers and experts outside the medical field. Our cover story in this issue features a shining example of what can be achieved from such partnerships: More than a decade ago, Dr. Leonard S. Marks began working with bioengineers in the UCLA Samueli School of Engineering on a new direction for prostate cancer evaluation and treatment, combining the sensitivity of magnetic resonance imaging (MRI) with the convenience and real-time benefits of ultrasound. This image-fusion biopsy approach has greatly increased the accuracy of prostate cancer diagnosis, while providing the ability to treat certain intermediate-risk patients with focal therapy, a less-invasive alternative to traditional surgery or radiation therapy.

Few universities can match UCLA in its breadth of expertise and its culture of multidisciplinary collaboration.

Dr. Marks and his team have helped to spearhead these major advances by leveraging an advantage enjoyed by only a handful of urology departments in the nation: easy access to a world-class engineering school, located just a short walk away. Few universities can match UCLA in its breadth of expertise and its culture of multidisciplinary collaboration; moreover, many top university medical centers are located away from the campus. The ability to bring the intellectual creativity of top engineering minds to real-world clinical issues represents a tremendous benefit for our faculty — and Dr. Marks is one of several who have embraced the opportunity, with highly encouraging results. Dr. Renea Sturm is working with engineering colleagues on a "Bio-Zipper" — a biodegradable microneedle for tissue closure following urethra repair surgery — as well as on 3D printing of urethras to potentially assist in the treatment of hypospadias, in which the urethra of newborn boys is incompletely formed. Dr. Sriram Eleswarapu is teaming with a group of bioengineers on research that employs 3D printing and imaging to assist in repairing the penises of children born with Peyronie's disease. Dr. Joseph Shirk and his bioengineering colleagues are developing 3D imaging tools that can assist in surgical planning for kidney and prostate cancer.

These types of collaborations — not only with engineering, but also across the UCLA campus as well as within the UCLA Health enterprise — serve as important lessons for our trainees on the value of multidisciplinary research. As we tackle the complex clinical issues affecting our patients, we are fortunate to be in the position to draw from the diverse perspectives and wealth of expertise that surrounds us, and to have forward-thinking faculty who recognize the opportunity and are making the most of it.

Mark S. Litwin, MD, MPH Professor and Chair, UCLA Urology

DONOR SPOTLIGHT

Alice and David Alkosser



hen Alice and David Alkosser learned about the prostate cancer work of UCLA Urology's Dr. Leonard S. Marks and his multidisciplinary team, they knew it was research they wanted to support.

"Dr. Marks told us about how this program of image-fusion biopsy and focal therapy was improving quality of life through more accurate diagnosis and either active surveillance or less-invasive treatment for many patients who, in the past, would have required radical prostatectomy or radiation therapy," David Alkosser recalls. "This is a disease that affects many men around my age, and we saw a chance to make a difference by helping to fund this research."

David Alkosser studied engineering at Cal Poly and started his career as an industrial engineer while always maintaining an entrepreneurial eye. His wife, Alice, studied food chemistry at UC Davis, where she developed an interest in wine and included viticulture and enology as part of her studies. Together, they began successful real estate businesses that now span several states — and in 2009, they established Shadybrook Estate Winery in Napa, California, which has been ranked by Yelp as the top winery in the state.

"My wife and I started with very little and have been blessed with great success in our businesses," David Alkosser says. "We both feel strongly that it is important to give back to work such as this that can help many people."

Kudos

Division has achieved national ranking status in the 2022 U.S. News & World Report Honor Roll. The program, under division chief Dr. Steve Lerman, Dr. Jennifer Singer, and Dr. Renea Sturm, is one of seven subspecialties within the UCLA Mattel Children's Hospital to be listed among the nation's best in the annual Best Children's Hospitals rankings.

A multidisciplinary team including UCLA Urology faculty Drs. Robert E. Reiter and Joseph D. Shirk as well as others from surgery, physics, radiochemistry, nuclear medicine, and pathology was the first in the U.S. to use a miniature gamma probe, SENSEI, for robotic-assisted prostate cancer surgery. The team is pioneering radio-guided robotic surgery for prostate cancer, combining SENSEI and the prostate cancer-targeted imaging agent, Tc99m-PSMA, to intra-operatively find and remove cancer spread in pelvic lymph nodes. In the first case, the team successfully found and removed a tiny (>3mm) metastatic node identified on diagnostic imaging.

Dr. Stanley K. Frencher Jr., UCLA Urology associate clinical professor and director of urology at Martin Luther King, Jr., Community Health, has been selected as a 2023 fellow in the prestigious Aspen Institute Health Innovators Fellowship Program. The fellowship is designed for senior executives in health care who have already made a difference in the field and are ready to have an even greater impact through their commitment to collaboration with colleagues across the country to find viable solutions to improving the U.S. health care system.

Dr. Desiree Sanchez, UCLA Urology resident, along with UCLA Urology associate clinical professor Dr. Stanley K. Frencher Jr., and UCLA Urology chair Dr. Mark S. Litwin, had a manuscript, Moving Urologic Disparities Research From Evidence Synthesis to Translational Research: A Dynamic, Multidisciplinary Approach to Tackling Inequalities in Urology, published in *Urology*.

Dr. Joseph D. Shirk, UCLA Urology assistant professor, had his manuscript, Effect of 3-Dimensional, Virtual Reality Models for Surgical Planning of Robotic Prostatectomy on Trifecta Outcomes: A Randomized Clinical Trial, published in the Journal of Urology. Dr. Shirk's research showed that providing surgeons with 3D virtual reality models for surgical planning can help to achieve the critical "trifecta" outcomes of prostate cancer surgery: controlling the cancer while maintaining patients' sexual function and urinary continence. Co-authors included Drs. Robert Reiter, Eric M. Wallen, Ray Pak, Thomas Ahlering, Ketan K. Badani, and James R. Porter. This study was highlighted by the American Urological Association.

Dr. Brian Shuch, UCLA Urology associate professor, director of the Institute of Urologic Oncology Kidney Cancer Program, and Henry Alvin and Carrie L. Meinhardt Chair for Kidney Cancer Research, was elected to the UCLA Molecular Biology Institute at UCLA.

UCLA Urology Fourth-Year Residents Focus on Research

At the halfway point in their training, UCLA Urology residents step away from the clinics and operating rooms to spend a year conducting research. Following are the paths chosen by UCLA Urology's 2022-23 fourth-year residents:



Dr. Andre Belarmino is devoting his fourth year to leading the research endeavors of the Men's Clinic at UCLA, under the mentorship and guidance of **Drs. Jesse Mills** and **Sriram Eleswarapu**, UCLA Urology faculty members. There, he will focus on identifying causes and possible therapeutic interventions for

male factor infertility. His main project utilizes a mail-in semen analysis kit to assess baseline rates of DNA fragmentation among fertile and sub-fertile cohorts. Dr. Belarmino will collaborate with Fellow Health in its DNA fragmentation test and mail-in semen kits, and will work on projects examining the cost-effectiveness and compliance of mail-in semen testing in the post-vasectomy patient.

"My goal for this research year is to further my knowledge of infertility and andrology, and better understand how medical startups can integrate with academic medicine to advance health care," Dr. Belarmino says.



Dr. Cindy Gu is spending her research year investigating new diagnostic tools to better understand and treat patients afflicted with interstitial cystitis or bladder pain syndrome (IC/BPS), under the guidance and mentorship of **Dr. A. Lenore Ackerman**, UCLA Urology assistant professor and director of research for

the Division of Female Pelvic Medicine and Reconstructive Surgery.

"A major barrier to effectively studying and treating IC/BPS is that it's a diagnosis of exclusion, lacking objective diagnostic measures," Dr. Gu explains. Her research project aims to better categorize and identify clinical phenotypes of IC/BPS through objective measures by using machine-learning approaches and identifying unique urinary microbiome groups. "We often see IC/BPS patients in clinic and they can be some of the most difficult patients to treat because we just don't know enough about them," Dr. Gu says. "Treatments courses are often prolonged because it requires a lot of trial and error, as each patient's symptoms are unique. Through better diagnostic tools and more accurate categorization of IC/BPS patients, future treatments and research can be tailored appropriately and accurately."



For her research year, **Dr. Lin Lin** is working with **Dr. Brian Shuch**, UCLA Urology associate professor, director of the Institute of Urologic Oncology Kidney Cancer Program, and Henry Alvin and Carrie L. Meinhardt Chair for Kidney Cancer Research; and **Dr. David Shackelford**, associate professor in

the Division of Pulmonary and Critical Care Medicine and an expert in signal transduction and cancer metabolism, to study cell metabolism of a common type of kidney tumor called oncocytoma. Using next-generation sequencing, gene expression analysis, and metabolic functional assays, the team aims to characterize the metabolic alterations in oncocytomas.

"Renal oncocytoma is one of the most commonly encountered benign renal tumors, and currently we are unable to differentiate these lesions from malignant kidney cancers, which leads to unnecessary treatment and tremendous health care costs," Dr. Lin explains. "We know oncocytomas are densely packed with mitochondria, where the biochemical processes of respiration and energy production occur; given that many cancers have mitochondrial defects, I hope this work will be a critical step toward understanding a wide range of pathologies in urologic cancers."



Dr. Grace Sollender is spending her research year exploring the experiences of patients and their families with the diagnosis and management of adolescent varicocele. Under the primary mentorship of **Dr. Eleswarapu** from The Men's Clinic at UCLA, with UCLA Urology faculty members **Drs. Jennifer Singer**

and **Christopher Saigal** as co-mentors, she will employ qualitative research methods to elicit core themes that inform decision-making.

"There is controversy in the field of pediatric urology regarding which adolescents may benefit from treatment of their varicoceles," Dr. Sollender notes. "To better counsel patients and their families on how to proceed after diagnosis of a varicocele, this project aims to identify key factors at play when families are making this decision. Ultimately, our goal is to improve the patient and family experience."

During residency, Dr. Sollender's clinical work has focused on understanding the importance of the family perspective as a key component of disease management in pediatric urology. "To this end, I hope this work will be an initial step in sparking a career dedicated to taking care of pediatric patients and their families," she says.





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UCLA Health hospitals in Westwood and Santa Monica placed # 5 in the nation in the 2022-23 U.S. News and World Report rankings.



The Men's Clinic at UCLA

DID YOU KNOW?

"Good" bacteria and "bad" bacteria may contribute to semen quality and male fertility outcomes. Researchers at the Men's Clinic at UCLA have launched the Semen Microbiome Project, an active clinical trial to study these bacterial effects on fertility. Results could lead to targeted, microbiome-based therapies to improve fertility outcomes.



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