

UROLOGY

AT YALE | 2018

**Collaboration
& Innovation at Work**



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"As we look ahead to 2018, we will continue to bring the best minds in urology together to deliver patient-centric, innovative care to our patients, their families, and our field."

- Peter G. Schulam, MD, PhD

I am pleased to introduce to you our new annual publication, *Urology at Yale*. Born from a desire to share the impact of our work with our colleagues, counterparts, patients and friends, we hope *Urology at Yale* provides you with a snapshot into the meaningful and innovative work happening here in New Haven.

In this inaugural issue, you will learn about the goals Dr. Leslie Rickey has in year three of her five-year NIH grant to promote and destigmatize conversation around women's bladder health. Dr. Preston Sprenkle is pushing the boundaries to improve imaging of the prostate for precise diagnosis for men with prostate cancer. Dr. Dinesh Singh and the stone team take a multidisciplinary approach to treatment and prevention of kidney stones. Genomic profiling of renal tumors has given patients of Dr. Brian Shuch new hope, and we explain why. The rapidly-growing Gender Affirming Program led by Dr. Stan Honig is opening doors for transgender patients in Connecticut and across New England.

Growth has been a recurring theme since I joined Yale University as the Chair of Urology in 2012. It was our priority to grow and expand the department to meet the needs of our patients, and we certainly have met that challenge. Our team of physicians, scientists, and advanced practice providers has grown to 44 since I arrived, which is an increase of more than 150 percent, and our faculty recruitment has allowed us to continue to add many talented individuals. In parallel, patient visits have increased more than 1,200 percent since 2013. As part of our commitment to train future leaders, our residency program has grown from two to three residents per year, with the hope to increase again in the near future.

As we look ahead to 2018, we will continue to bring the best minds in urology together to deliver patient-centric, innovative care to our patients, their families, and our field.

Most sincerely,

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Collaboration & Innovation at Work

Kidney stones are formed to develop in nearly one in every ten Americans. Often, this results in severe pain and a trip to the emergency room, leading to missed work and high healthcare expenditures. The rate of kidney stone occurrences has risen in recent years, and as a result, the economic impact of kidney stones – direct treatment and indirect costs from lost worker productivity – has exceeded \$5 billion annually. But the Yale Stone Team believes kidney stones can be a preventable disease.

“We believe failure of patients to prevent stones is not only due to a lack of implementation of standard hydration and diet recommendations, but rather a lack of education and identification of individualized risk factors for stones,” suggested Dr. Dinesh Singh, Assistant Professor, Urology and Director, Endourology and Laparoscopy.

Dr. Singh and the other members of Yale’s stone team deploy a collaborative and proactive approach to treatment. Urology, nephrology, and nutrition experts work together to help patients with treatment, teaching them how to manage their existing stones and providing strategies to reduce the risk of future kidney stone development. Once one stone has formed, odds increase to 50-50 that another will develop within the next ten years. Dr. Singh and his team are working to make that probability more favorable to the patient.

When patients arrive for their appointment, it is a “one-stop shop” according to Dr. Singh. They meet with physicians representing each aspect of the clinic team, receiving a unified, but unique message from each physician based on their specialty. The urologists, Drs. Dinesh Singh and Piruz Motamedenia, Assistant Professor of Urology, use innovative, low radiation imaging to identify stones and best decide what options are available for treatment. If surgery is needed, priority is placed on performing state-of-the-art procedures that are minimally invasive for the patient and offer the optimal outcome. Dr. Neera Dahl, Associate Professor, Medicine (Nephrology), studies the genetics

of patient stones and provides options for patients to managing their care with medicine in combination with diet. Nearly 25% of the genetic component to stones is familial, and when a patient has a first degree relative (parent, sibling, or child) with stones, their own risk increases significantly. Dr. Dahl uses a battery of tests from both urine and serum to identify the patient’s individual risk factors for stones and thus, can modify that patient’s risk for future stones. Amy Bragagnini, RD, Clinical Dietician, provides dietary recommendations based on the context of all medical issues present, including obesity and diabetes, two common issues found in kidney stone patients.

Expanding beyond the clinical setting, the Yale Stone Research Team, a collaboration representing urology, emergency medicine, biostatistics, and radiology, is leading efforts to better manage patients who present with flank pain, to better identify patients who need imaging, and to reduce the harms of radiation in stone patients who are often subjected to multiple and sometimes high dose CT scans.

The team discovered five factors most predictive of a kidney stone: Sex of the patient, Timing or duration of their pain, Origin or race of the patient, Nausea or vomiting symptoms, and Erythrocytes or blood in the patient’s urine, which is known as a “STONE score.” These factors were determined to accurately and reliably predict which patients do and do not have a stone present in their ureter, based on their STONE score. This groundbreaking discovery led the team to publish their findings in *The BMJ* in 2014.

Two years later in 2016, a group of physicians and researchers from Massachusetts General Hospital, who, after applying their own patient data to the STONE algorithm and found the same results, published an external validation of the STONE score. The STONE score is used in emergency rooms at Yale New Haven Hospital and its application is increasing nationwide.

“Not only was the STONE score an exceptional development by our team, but receiving external validation from our counterparts at Mass General was especially exciting,” said Dr. Singh.

The Yale Stone Research Team next took this study one step further and explored the concept of using the STONE score to filter patients away from unnecessary high-dose CT scans and instead to ultra low-dose CT scans.

In a randomized study of more than 250 patients, they determined that those who received the low dose scans received nearly the same diagnosis as patients given the standard scan. 2-5% of stones were missed with the low dose procedure, but were found to be 5MM or less in size and thus, non-clinically important.

The number of high-dose CT scans performed on kidney stone patients has skyrocketed in part due to an overall increase in patients developing stones, and simply, because of the indiscriminate use of CT scans. In 2007, the rate of CT scans performed in the U.S. was nearly 228 per 1,000 people, more than double the rate in Canada and four times the rate in the United Kingdom. This has led to an estimated 1 in every 500 to 1 in every 1,500 patients being put at risk of developing additional malignancies from radiation exposure.

Yale is an ardent advocate in its efforts to increase the utilization of low dose CT scans by publishing research articles with randomized studies as well as giving lectures across the US. Its efforts have not gone unrecognized. When the study results were published, only 2% of academic healthcare institutions were utilizing low dose scans, and the most recent estimate shows an increase of up to 8%.

The collaborative efforts led by the Yale Stone Disease Team and the Stone Research Team have moved Yale to the forefront of stone disease diagnosis and treatment. And as a result, patients are the benefactors. “They truly become our patients,” said Dr. Singh. “We are shepherds of their stones and it is our duty to provide the latest in technology and be surgically state-of-the-art.”



At their first appointment, patients meet with physicians representing each aspect of the clinic team, receiving a unified, but unique message.

Leslie Rickey, MPH, MD

This is a large, public health issue that affects almost every girl or woman – it affects their physical and emotional health.

Yale Joins National Effort to Improve Women's Bladder Health

Dr. Leslie Rickey treats women for a constellation of lower urinary tract symptoms, including incontinence. Ideally, she would like to have ways to better identify girls and women at risk and intervene earlier, but research has focused almost exclusively on developing better treatments rather than maintaining good bladder health. Dr. Rickey is committed to changing that.

The Associate Professor of Urology recruited a multidisciplinary team and successfully competed to make Yale one of seven clinical sites in the nation for the Prevention of Lower Urinary Tract Symptoms (PLUS) consortium. The National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health is funding the first large-scale study of bladder health in women. The PLUS consortium brings together a diverse group of investigators from the medical and social sciences that includes epidemiologists, clinicians, and prevention specialists. The group is taking the unique approach of using a public health lens to shift research and practice towards promotion of bladder health.

“Although lower urinary tract issues affect up to 1 in 3 women, bladder health isn't something that people talk about,” said Dr. Rickey. She regularly sees patients who have coped long-term with incontinence by using pads, limiting fluid intake, avoiding exercise and travel, or by mapping out the bathrooms wherever they need to be. “Sooner or later, the bladder dysfunction overwhelms their ability to compensate for it,” she said.

“I don't want to downplay the extremely effective treatments we have for people with incontinence or overactive bladder,” said Dr.

Rickey. “I utilize both non-surgical treatments and minimally invasive procedures for women that can really improve their quality of life.” However, she believes that there are women for whom earlier detection and intervention might prevent the need for a surgery down the line.

Dr. Rickey would like bladder problems to be destigmatized to the point where patients seek care earlier, when simpler remedies may solve the problem. Even more so, she wants to be able to offer advice on prevention. At present, however, little is known about the factors that protect women from bladder problems. In fact, one of the first goals of the project is to define what a healthy bladder is. No such standard exists now.

PLUS researchers hope to make discoveries that will substantially change the way clinicians support women, but those findings should not be confined to professional journals. “One of the things I really like about what I do is education,” said Dr. Rickey. “The level of lower urinary tract information housed in the scientific community that doesn't get well disseminated to the public is just stunning.” For this reason, the PLUS consortium has prioritized developing a robust community engagement network in order for community members to have input on everything from research constructs to language used in survey items and eventually, help with getting the message across to the public. There could even be implications for policy change, said Dr. Rickey, such as workplace rules about bathroom breaks or equitable toilet availability in work places, schools, and public spaces.

Dr. Rickey formed a team of people who had never worked together before but quickly bonded around the task. “I think it's huge. It

affects so many women throughout their lives and it can really limit the activities that women can be involved in later in their lives,” said Jessica Lewis, Deputy Director of Pregnancy Research at the Yale School of Public Health. “Our hope is that once women become more aware of their bladder health and realize there are things they can do, they will concentrate on those pieces of behaviors or environmental stressors that are modifiable.”

Each of the PLUS sites is conducting focus groups to learn more about women's current knowledge and experience with bladder health. At Yale, the focus groups will concentrate on young women from the New Haven area. “It takes some skill to get young people to speak about a topic that they've never thought about,” said Dr. Deepa Camenga. Though Dr. Camenga, whose expertise is in adolescent health, has an office close to Dr. Rickey's, they had never met before they began discussing the possibility of making Yale a PLUS site. One day, Dr. Camenga looked up from her desk to see a woman in scrubs, Dr. Rickey, a bit flushed because she'd just run from the operating room to get in a conversation between surgeries.

“Are you Doctor Camenga? I've been trying to meet you. Do you have a few minutes to talk to me?” she asked. Dr. Camenga laughs at the memory. “I thought, ‘Wow, that woman is excited.’” She continued: “I think this highlights the great diversity of experience at Yale. We were awarded this because Dr. Rickey was able to bring together people with very diverse experiences.”

Three years into the project, Dr. Rickey remains excited. “This is a large, public health issue that affects almost every girl or woman – it affects their physical and emotional health.”

The Brain-Bladder Connection

Erik and Salina Andersen were at wits' end. Since the age of 3 ½, their son, Alek, suffered from torturous spasms. Sudden, intense pain in his bladder area would drop their son to his knees 20 to 30 times a day and trigger incontinence. "Alek called them 'twisties,'" said Erik Andersen. "You could see the pain in his face."

Their search for answers for Alek's 'twisties' led the Chicago couple to multiple specialists, whose conflicting diagnoses offered no relief from the debilitating episodes. After 2 ½ years of endless frustration, the Andersens finally found the help they needed from Israel Franco, MD, Director of the Yale New Haven Children's Bladder and Continence Program.

Throughout his three decades of leadership in pediatric incontinence, Dr. Franco has repeatedly revolutionized the field by championing the link between the brain and bladder in urinary incontinence and had sought non-invasive methods as a means—to reset the brain-bladder connection and restore his young patients' continence and confidence.

It now seems a bit ironic that Dr. Franco was first drawn to pediatric urology because of its opportunities to perform complex surgeries. As he learned more about his patients, he concluded that the standard diagnostic and treatment protocols were failing them. "A lot of the things we were doing were not evidence-based," he explained. "There was a clear-cut lack of anyone who had any true insights. I became that person, simply because I was the one seeing these patients. I started thinking outside the box to try to change the way we approach the problem."

His interest dovetailed perfectly with advancements in medical technology. Dr. Franco was an early adopter of laparoscopic and robotic bladder surgery, which minimized the physical

hardship and recovery time for his young patients. He was among the earliest practitioners of biofeedback therapy, which attunes patients to the sensation of the proper muscle relaxation necessary for controlled urination.

Dr. Franco's practice took another giant leap forward with the advent of functional MRI.

"It opened up the field by showing us what was going on in the brain," he said. "It became clear that the sites of the brain associated with the voiding function were the same sites associated with what we call 'syndrome mix,' or executive-function disorders such as ADD, OCD, anxiety, depression, etc. We started exploring whether there was a link between the two."

Dr. Franco's research into the mind-bladder connection marked a paradigm shift in the field of pediatric incontinence. "Prior to then, everything was the bladder, bladder, bladder," he said. "But the bladder doesn't stretch itself out if the brain doesn't let it. In the end it's an interplay of bladder physiology, neurophysiology, the gastrointestinal tract, and psychiatry. They are four points in a square that all come together. You need knowledge of all of them."

The Yale New Haven Children's Bladder and Continence Program helps children age 5 to 21, like Alek, gain bladder control. When families like the Andersens first arrive, Dr. Franco reviews an extensive questionnaire with them that enables him to quickly distinguish if the core issue is one of emptying, urgency, or sensation. "We were very grateful that Dr. Franco spent quite a bit of time with us," Mr. Andersen said. "He was interested in really understanding Alek's total history."

Dr. Franco concluded that Alek's bladder spasms were caused by an inability to modulate signals from the bladder appropriate in his brain.

He had already failed novel medical treatments that his urologist had tried at the suggestion of Dr. Franco. Instead of a continuing down a path of standard medications, Dr. Franco suggested they first try TENS. This non-invasive treatment is most often used for back pain, but Dr. Franco has incorporated its use in his treatment armamentarium with great success.

In TENS, a small battery-operated device transmits a low-voltage electric current through two electrodes adhered to the skin. For Alek and other pediatric urology patients, the electrodes are placed over the "dimples" on both sides of the lower spine, where the sacral nerve lies close to the surface. The treatment lasts 30 to 45 minutes each day. "It seems that those sites in the brain associated with the control of the urge to void are being activated," Dr. Franco explained. "Somehow, through neuroplasticity changes in the brain, we're able to reset the sensation in their brain that allows the child to begin to stay dry or fix the way they urinate."

Typically, after eight weeks of TENS, parents will see a sudden, dramatic improvement in their child's bladder control. But, Alek's case was not typical. "In one week, our son was cured," Mr. Andersen said. "Dr. Franco transformed our lives. Alek was cured just in time for first grade. He's such an outgoing and friendly kid/boy, and he is finally able to engage in social activities in a way he was afraid to before."

As Alek continues his daily at-home TENS treatment, Dr. Franco continues to explore the mind-bladder connection. "I was drawn to work at Yale because of the research potential here," he said. "Yale has 13 MRI machines just for research. And we'll be able to do genetic testing as well. I knew Yale was the ideal place for me to be able to study these children. We are dedicated to taking care of these children."

Israel Franco, MD

Dr. Franco's research marked a paradigm shift in the field. In the end it's an interplay of bladder physiology, neurophysiology, the gastrointestinal tract, and psychiatry.



Stanton Honig, MD

We're dedicated to being a state-of-the-art center for gender affirming surgery.

Surgery - and an Environment - that Breaks New Ground

Yale was the first medical center in New England to provide gender affirming surgery for male-to-female transgender patients and remains the only site in Connecticut to offer the procedure. The Director of the Gender Affirming Surgery Program, Dr. Stanton Honig, is most proud of the environment that his team has created.

"We have worked very hard to make our center a place where transgender patients feel comfortable, because that's what they deserve," said Dr. Honig. "One of the things that you have to realize is this population historically has not been treated well by the medical profession."

The Program provides training for everyone - from the clinical receptionists who answer the phones to the attending physicians - to create a welcoming environment for transgender patients.

"A lot of our patients haven't received proper healthcare for most of their lives," said Meghan Curran, RN, assistant patient services manager for the Department of Urology. She described an all-too-common scenario in a doctor's office of a transgender woman wearing a dress and getting the "third degree" when her driver's license showed a different first name and gender - and never making it past the waiting room for her appointment.

Listening to his patients was what led Dr. Honig to begin offering gender affirming "bottom" surgery. A reconstructive urologist, Dr. Honig began performing the surgeries when patients themselves requested them. "The best way to explain it is: each part of the operation is something that we already do in

reconstructive urology," he explained. The inverted skin of the former penis becomes a vagina. Making a new clitoris with good sensation is similar to other operations we do on the penis. Dr. Honig has been performing the operations together with a plastic surgeon, and together, they are dedicated to providing state of the art surgical care.

The Program follows the guidelines of World Professional Association of Transgender Health (WPATH). Patients must be 18, have care letters from mental health professionals attesting that they understand the procedure is irreversible, and understand the risks and nature of the surgical transition. Patients must also be on continuous hormonal therapy and dress in the gender that they feel most comfortable for at least one year. Most, said Dr. Honig, have been living as transgender women for much longer.

Dr. Honig is also Director of Yale's Male Reproductive Health Program and can assist his patients to freeze their sperm to preserve their ability to have biological children, if they so desire. Care is long-term, in keeping with the patients' unique needs. For example, the women will need the same prostate screenings as male patients following their surgery.

Care is also holistic and includes an assessment by the team's social worker, Fentyshia Daniels, LMSW. The discrimination that transgender patients frequently experience causes many to be separated from family, suffer economically, or experience mental health challenges like depression and substance abuse. When counseling her patients, Ms. Daniels starts with basics, such as connecting

patients to transportation, housing and other necessities. She also tries to "think outside the box" to help patients build a support network of extended families and friends. Soon the program will provide a patient support group.

The Gender Affirming Program surgery team is also working to arrange affordable patient lodging near the medical center. Many patients travel from out of state to have the surgery at Yale and all must return for follow up visits within a week after the procedure.

"We're continuing to learn and improve our technique, and we're dedicated to being a state of art center for gender affirming surgery," Dr. Honig said. He travels to share experiences with other urologists performing gender affirming surgery and expands the field through his leadership on the American Urological Association's transgender education working group.

An estimated 1.4 million adults in the United States identify as transgender. Though they will choose from a variety of surgeries, or choose no surgery at all, the need for more urologists trained in gender affirming surgery is clear, particularly as changes in insurance reimbursement have made the surgery a possibility for more people, especially in Connecticut, explained Dr. Honig.

But he also emphasized that training clinicians in the interpersonal side of the practice is every bit as important as passing on technical and surgical knowledge. "It used to be called gender confirming surgery. Nobody needs to confirm their gender! Patients affirm their own gender and call it gender affirming surgery because that's what it is. Affirming," he said.

Advances in the Detection of Prostate Cancer

Aside from skin cancer, the most common site for cancer in American men is the prostate, with an estimated 160,000 new cases last year [ed.—2017]. Prostate cancer is also the third most deadly for American men, with more than 26,000 deaths in 2017. Yet the standard diagnostic method of searching for prostate tumors lags behind technologies used in other cancers. Researchers in the Yale School of Medicine's Department of Urology are working to change that. They are developing imaging tools to give surgeons and radiologists a clearer picture of prostate cancers. Clearer images translate into more accurate diagnoses and more precise targeting of the tumors.

"We're working to push the field forward," said Preston C. Sprenkle, MD, Assistant Professor of Urology and Chief of the Division of Urology at the VA Connecticut Healthcare System. The field needs a push. If a urologist wants to determine whether a patient has prostate cancer, the standard procedure is to use ultrasound to locate the organ and then to insert biopsy needles that take random samples from the prostate.

"It's as if you can see an apple, and you know there's a worm in there somewhere, so you put darts in to get it," said Dr. Sprenkle. "But since you don't know where the worm is, you have to guess—you evenly space the darts and hope you hit it." This haphazard method has predictably mediocre results, missing about a third of all prostate cancers.

Until recently, the prostate was the only solid organ where physicians didn't have access to imaging technology to see inside it. That has started to change thanks to new systems that blend ultrasound with magnetic resonance (MR), a combination known as MR-US fusion. Yale was an early adopter of the

technology. Using software algorithms, MR-US fuses the two different images to capitalize on information from both. The resulting 3-D images enable physicians to identify suspicious lesions in specific locations within the prostate.

"By doing that," explained Dr. Sprenkle, "we know where to place our needle to sample the tissue. These targeted biopsies have increased our detection of higher-risk prostate cancers."

MR-US fusion isn't yet the standard for several reasons. First, adding MR to the biopsy adds cost, which some hospitals and insurance companies resist. Second, fusion technology is still new, and data about its benefits and cost effectiveness aren't yet conclusive. And third, though MR-US is an immense improvement over ultrasound alone, the two images fuse imperfectly, leaving room for errors in diagnosis. Not all practices have the expertise and experience to create the fused images and interpret them correctly.

Making interpretation easier is where Dr. Sprenkle saw an opportunity. He is part of a multidisciplinary group at Yale Cancer Center that collaborates on research related to prostate cancer. He proposed a project to improve the computer system, called Artemis, that does the fusion imagery. He began working with Xenophon Papademetris, PhD, Professor of Imaging Processing and Analysis, who involved the makers of Artemis. The project is funded by the NIH through its Small Business Technology Transfer Program (STTR).

"Part of the challenge is that images from MR and ultrasound look very different," said Dr. Papademetris. "The second problem is that the prostate doesn't have the same shape in an MRI as in ultrasound, because the MRI is done with the patient lying on his back in a scanner, and the ultrasound is done by inserting a probe through

the rectum, so it's pushing against the prostate, which causes some compression-deformation. The Artemis system stretches and shrinks and grows one surface to make it fit into the other, and then you cut in the rest of the image."

The partial deformation of the prostate during ultrasound introduces a degree of imprecision that can lead to missed lesions. Drs. Papademetris and Sprenkle are trying to reduce that imprecision by translating clinical experience—Dr. Sprenkle has done about 800 biopsies using MR-US—and data from previous patients into better software that calculates and corrects for probable deformations, and thus creates a more accurate image.

The new software is now being validated. Drs. Sprenkle and Papademetris expect to test it in a clinical trial early this year [ed.—2018], along with partners at Stanford University. The ultimate goal is to make fusion imaging so precise that it automates interpretation and eliminates errors.

Dr. Sprenkle is also a pioneer in several kinds of "focal therapy," a targeted approach made possible by MR images, which reveal small lesions that can be treated using a variety of energy sources, saving patients from the severe side effects caused by intensive radiation or removal of the entire prostate.

All of this reflects the commitment of Dr. Sprenkle, Dr. Papademetris, and their colleagues to deploy better ways of finding and defeating prostate cancer. "It takes a multidisciplinary effort," said Dr. Sprenkle. "We have outstanding nationally-recognized radiologists and outstanding nationally-recognized pathologists. We are very experienced, and experience matters. In biopsies, being a millimeter or two from where the cancer is located can make a significant difference."

Preston Sprenkle, MD

Until recently, the prostate was the only solid organ where physicians didn't have access to imaging technology to see inside it. Yale was an early adopter of new technology.

Brian Shuch, MD

Some renal tumors may not need to have surgery immediately. Some can be faithfully observed up to a certain size.

Codebreaker: Profiling Kidney Cancers

Brian Shuch, MD, uses genetic profiling to guide the management of renal tumors. Among the many roles that physicians assume is that of interpreter. Doctors must be adept at interpreting a patient's symptoms and test results to reach the right diagnosis. Then they must translate that diagnosis into terms that a patient can understand.

In his cutting-edge work treating patients with kidney cancers, Brian Shuch, MD, Assistant Professor of Urology and of Radiology and Biomedical Imaging, has proven himself a gifted interpreter. By evaluating tumors not by shape and size—as has been standard protocol for decades—but by genetic profile, Dr. Shuch has launched an entirely new dialogue about the identification and treatment of these cancers. But as his patients can attest, Dr. Shuch also has a talent for conveying the results of this incredibly complex genetic testing with simple analogies that help them clearly understand their diagnosis and treatment options.

A tumor's genetic profile reveals crucial information: the type of kidney tumor, whether it's benign or cancerous, what kind of kidney cancer, and how aggressive it is. "Some renal tumors may not need to have surgery immediately," he said. "Some can be faithfully observed up to a certain size." He considers these tumors to be "guppies"—not harmful—as compared to "sharks," which require immediate, aggressive treatment.

Before his consult with Dr. Shuch, patient Jerome Serling, DMD had already been diagnosed with presumptive renal cell carcinoma. The traditional protocol would be to remove the lesion or kidney. But Dr. Shuch first suggested Dr. Serling undergo a renal mass biopsy with genomic profiling to determine if the lesion was, in fact, dangerous. To Dr. Serling's great relief, his lesion was a "guppy." There were no chromosomal changes

that would suggest renal cell carcinoma and this tumor had all the characteristics of a common benign tumor. Dr. Shuch and Dr. Serling agreed that close monitoring of the lesion was the best course of action. "Because of the genetic test, I was able to avoid surgery," Dr. Serling said. "I was very grateful for Dr. Shuch's use of the test and his keen clinical judgement."

With support from an \$800,000 NIH grant, Dr. Shuch is continuing his research on genetic profiling, focusing on the heterogeneity of small renal tumors. "Sometimes tumors can be a mixture of different types of cells," he explained. "It can be like a bag of M&Ms with different colors. We know that for small tumors, when you stick your hand in a bag and find a green M&M, then most of the bag is going to be green. But for large tumors, if you pull one sample, it might be a red M&M, but in the bag, there will likely be a lot more different colors."

"The importance of this to kidney cancer research is that, if you profile one part of the tumor and get an answer that this tumor is bad or good, you want to be sure that you are giving the patient the best idea of what is in the whole bag of M&Ms," he said. "You don't want to base your diagnosis on an incomplete sample."

Another aspect of integrating genetics to clinical care is how Dr. Shuch evaluates individuals with suspected hereditary forms of cancer. An estimated five to eight percent of kidney cancer patients have a strong hereditary or genetic component. Because of the rarity of these cancers, many caregivers are not familiar with the distinct symptoms associated with them. The median age of onset for hereditary kidney cancer is around 36—about 30 years younger than other kidney cancer patients. Instead of a single tumor, patients may have bilateral or multifocal tumors. A handful of the conditions have related dermatological symptoms. And in some families, there's a

history of the disease spanning back several generations.

Dr. Shuch and his colleagues at Smilow's Cancer Genetics and Prevention Program are on high alert for these red flags when they evaluate patients with urologic cancers including kidney cancer. "Unfortunately, most patients who have a genetic or hereditary component are never diagnosed," said Dr. Shuch, who leads the Program's Genitourinary Cancers Division. "In the cases when it is recognized, it's usually after the patient has had treatment and gone for genetic counseling. Most have had surgical management of the kidney cancer. If they had known their condition prior, surgery might have been avoided or different management strategies could have been employed."

As part of his evaluation, Dr. Shuch conducts a genetic screening panel of a patient's tumor. A Yale panel, developed by Dr. Shuch and colleagues, enables screening for the 15 known syndromes of hereditary kidney cancer with just one test. Yale is one of the first centers to promote such a panel for kidney cancer, which now is offered by a variety of genetic testing companies. Testing multiple genes at once significantly streamlines and expedites the diagnostic process. "Each of the known kidney cancer syndromes are linked to a specific gene of interest that may not be able to be identified clinically," he explained. "By casting a wider net and testing all the genes at once, we have a better chance of finding the cause of someone's predisposition."

Dr. Shuch's groundbreaking work on genetic profiling holds promise not only for his current patients but for their families as well. "We'll be able to screen their family members and children to detect a tumor before it causes a problem," he explained. "Because where do big problems come from? Little problems. If we can find it early and fix it, we can prevent them from having significant harm to their livelihood."

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