

NEPHROLOGY

Growing Expertise in Complement-Mediated Kidney Diseases

n a laboratory at Washington University School of Medicine, transplant nephrologist Anuja Java, MD, is working on identifying and treating rare kidney diseases. What she's focused on are complement-mediated diseases that include atypical hemolytic uremic syndrome (aHUS), thrombotic microangiopathy (TMA) and C3 glomerulopathy.

"The prevalence is low, maybe two or three people per million for aHUS, for example," says Java. "But I believe the prevalence may be low because these diseases are not widely recognized."

She is building upon breakthrough immunology research conducted at the School of Medicine over the past 40 years by her research mentor and now collaborator, rheumatologist John Atkinson, MD. "We are both excited about the field of complement immunology," Java says. "He is an expert in the role of the complement system in infectious, autoimmune and inflammatory diseases, such as lupus and age-related macular degeneration. In our collaborative research, we have been looking at gene mutations and deficient proteins along the complement pathway that predispose individuals to rare kidney diseases."

A former fellow in WU's transplant nephrology program, Java was particularly interested in complement immunology and how genetic mutations along the complement pathway could impact the success or failure of kidney transplants.

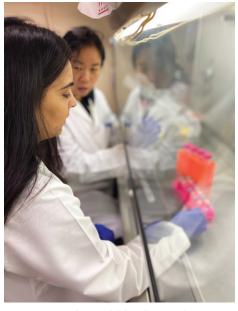
When evaluating patients for transplant, it is critical to know the underlying cause of their kidney failure since certain

diseases recur in the allograft and can lead to loss of the precious kidney. Atypical HUS, TMA and C3G have a high risk of recurrence after a kidney transplant.

"Knowing the underlying etiology allows us to use prophylactic treatment in some cases, monitor for disease recurrence closely and initiate treatment early in others," Java says. "Biopsies can confirm the presence of blood vessel damage or blood clots within the kidneys, which can be a hallmark of TMA. Our suspicions are raised when we see that, so we order genetic testing to assess if the problem could be a genetically-mediated disease."

Importantly, patients who developed kidney failure due to pregnancy-associated TMA or another secondary TMA whose evolution was unusually aggressive should also be evaluated for genetic causes.

Genetic variants can be identified in about 60 percent of cases, but most are characterized as of "uncertain significance," "likely pathogenic," or "likely benign." When that occurs, Java turns to her lab, actually manufacturing those specific gene mutations to confirm a patient's individual diagnosis and define treatment options — in other words, personalized medicine for these rare diseases. The manufacturing of these complement mutations and Java's work to conduct functional testing on the expressed protein is not done regularly anywhere else in the United States. As a result of her translational and transformative research, patients from across the country are being referred to Java.



Anuja Java, MD, along with lab technician Zheng Hu, manufactures novel gene mutations in her lab to define treatment options for complement-mediated diseases.

"We now have more than 75 people in our database for which we have identified their specific gene variant," says Java. "If this work wasn't accomplished, they might have undergone a kidney transplant but then, later, have recurrence of disease in the transplanted kidney and be diagnosed with kidney failure again."

Her timing in identifying these variants comes at a time when there is now an FDA-approved drug, eculizumab, to treat kidney patients with specific gene mutations who are diagnosed with aHUS. In addition, there are multiple drugs in the pipeline for other complement-mediated kidney diseases, includes C3G and IgA nephropathy.

Java now is leading a new and growing program on complement-mediated

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Message from the Chief



As we go to press the entire division is joining together in preparation for the COVID-19 pandemic. This is an unprecedented time and we are actively plan-

ning strategies to provide care for infected patients both in the hospital and in the community. I am deeply grateful for the resilience and engagement of the entire division and especially those caregivers who are on the front lines.

Despite the uncertainty ahead, I hope that this update will keep you apprised of the many activities in the division. As you will read in our front page story, we have established a subspecialty clinic for complement-mediated kidney diseases. This clinic arose from a strong interest in immunology and complement diseases by Anuja Java, MD. She has leveraged the strengths in

immunology and genomic testing found at Washington University School of Medicine into a program that offers transformative diagnostic testing for complement-mediated diseases. Her new clinic is the sixth subspecialty clinic in our division. We also have a growing onco-nephrology clinic, a lupus and glomerular disease clinic, a multidisciplinary kidney stone program, and dedicated clinics for nephrotic syndromes.

The variety of our clinical experiences enables the fellows in our training program to receive high quality, intensive training in a wide range of disciplines. They also can take advantage of our growing community-based clinics; most recently we opened an interventional nephrology clinic and an outpatient clinic for veterans in north St. Louis County.

We continue to expand our research endeavors. For the fifth year, the Division has awarded a Translational Innovation grant to a basic scientist and a clinical researcher in

the Division to collaborate on investigations that have the promise of translating results into better patient care or novel therapeutics. Recently Monica Chang-Panesso, MD, and colleagues published "FOXM1 Drives Proximal Tubule Proliferation During Repair from Acute Ischemic Kidney Injury" in the December 2019 Journal of Clinical Investigation. I encourage you to read the article and regularly check our news tab at nephrology.wustl.edu/news/ to keep in tune with all that we are doing in our Division.

I extend my best wishes for your health and your loved ones health during these difficult times.



Benjamin D. Humphreys, MD, PhD Joseph P. Friedman Professor and Chief Division of Nephrology Washington University School of Medicine

Thank You!

The Division of Nephrology thanks the following individuals who have generously donated to our division from October 2019 through February 2020:

Dr. Arvind and Ms. Dipika Garg Ms. Judith A. Douglas Mr. & Mrs. Joel and Susan Allen Mr. & Mrs. Martin E. Jaffe Dr. Richard M. Mazey Ms. Patricia M. McKevitt

Dr. John Mellas Dr. Didier Portilla Mr. & Mrs. Terrance Dwaine and Karen Lee Sell Dr. Thomas Ralph Pohlman

Support the Division of Nephrology

If you would like to support our research and teaching mission or contribute to the Division of Nephrology's programs and services, please send your contribution to: Washington University in St. Louis Office of Medical Alumni and Development Attn: Rachel A. Hartmann 7425 Forsyth Blvd. Campus Box 1247 St. Louis, MO 63105

You may also contact Rachel A. Hartmann directly at 314-935-9715 or by email at rachel_hartmann@wustl.edu if you are considering supporting the Division through appreciated stocks, deferred giving, beneficiary plans or other assets.

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Fellowship Notes



By Tingting Li, MD, MSCI, **Association Program Director, Nephrology** Fellowship Program

Expanded Leadership Team

In a move to enhance the educational experience and to increase career development and mentoring opportunities for our nephrology fellows, the Fellowship Program has once again expanded its leadership team. The team, which included Steven Cheng, MD, Seth Goldberg, MD,

and myself, recently added Frank O'Brien, MD as an associate program director to oversee the educational curriculum.

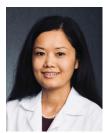
Steven remains the program director, handling administration and policy. Seth oversees clinical rotations and fellow competency assessment. Frank, who has developed peritoneal and hemodialysis curricula for our trainees, steps into the larger role of supervising fellowship curriculum development and revamping the educational conferences.

I will continue my role as the Associate Program Director of Clinical Research and Career development, providing guidance and mentorship to the fellows. In addition to the annual career development retreat, which was launched successfully last year

(and profiled in the last newsletter), I will explore elective options tailored toward fellows' interests and provide fellows with institutional and outside resources to support their professional growth. I will also develop a wellness curriculum for fellows to ensure that they have the optimal learning environment and work-life balance.

The expansion of the program leadership reflects our ongoing commitment to fellowship education, well-being, and career development. We are proud of our standing as one of the premier nephrology fellowship programs in the country and we will continue to strive to provide an unparalleled training experience.

Gurung Joins Nephrology Fellowship



Reena Gurung, MD, has transferred from the Nephrology Fellowship Program at Loyola University Medical Center in Maywood, Ill. to the Washington University

Nephrology Fellowship Program. Gurung, who started as a first-year fellow in February of this year, earned her medical degree from the School of Medical Sciences at Kathmandu University in Nepal and completed a residency in internal medicine at St. Luke's Hospital in Chesterfield, MO.

In 2015, she joined the faculty of Washington University School of Medicine as an instructor in the Division of Hospital Medicine. She subsequently decided to pursue a fellowship in nephrology and, in 2019, was accepted into the Nephrology Fellowship at Loyola University. We are delighted that she is back in St. Louis and in our Division to further her training in nephrology.

Welcome New Fellows!

We had a stellar match for the fellows who join our division in July. And we have to say, they bring with them a diverse background of experience, dedication and fun! Read more about them under our News tab at nephrology.wustl.edu.



Maryam Seelam, MBBS Yale University, Waterbury, CT



Jason Cummings, MD Florida Atlantic University Boca Raton, FL



Hassan Iftikhar, MBBS Seton Hall University Trenton, NJ



Bharat Neelam Raju, MD Good Samaritan TriHealth Cincinnati, OH



Gaurav Rajashekar, **MBBS** Texas Tech University Odessa, TX

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kidney diseases. She sees these patients in her specialty complement clinic to provide consultation on the diagnosis, interpretation of genetic results, risk of recurrence after kidney transplant and to help decide treatment options.

Alumni Connections

Sharina Belani, MD

The Permanente Medical Group San Rafael, CA Nephrology Fellow, 2002-2005

Sharina Belani, MD, says that her time as a nephrology fellow at Washington University School of Medicine not only was the "ultimate opportunity" to obtain a wide range of clinical expertise, but also served as a foundation for her to build what she now calls "one of the best jobs" — serving as a Chair of Chiefs in Nephrology for The Permanente Medical Group (TPMG), an integrated care system in Northern California that is one of the largest physician-led medical groups in the United States.

"I started as 100 percent clinical when I first joined the organization in 2005," she says. "Now, about a third of my role is serving as the nephrology strategy lead for Northern California, which includes inpatient and outpatient nephrology services, subspecialty nephrology services, and kidney transplant. We focus on three pillars of care delivery strategy, which is improving overall operational excellence, enhancing the patient care experience, and focusing on opportunities to improve the joy of being physicians in health care. Ultimately, we want to empower our Nephrologists to steward care delivery and develop operational efficiencies that lower the cost of healthcare. For example, we lead the nation in the incidence and prevalence of peritoneal dialysis and optimally starting dialysis without a hemodialysis catheter. In addition, our Nephrologists partner with our extensive medical group to move upstream to identify early CKD and downstream to provide primary palliative care and advance care planning decisions specific to the life sustaining treatment of dialysis"

With 9,000 physicians representing 70 specialties and subspecialties within the medical group, TPMG has more than 80 nephrologists. In addition to seeing patients with kidney diseases and complications, the team cares for 6,000 dialysis patients annually, and follows 3,000 post-kidney transplant patients each year.

"The fellowship at Washington University gave me an amazing degree of confidence as I started my career because I participated in an extensive variety of clinical opportunities, such as tertiary nephrology care and kidney transplant," she says. "Along with that, I had great mentors who showed me not only their passion for patient care but also what quality care can look like."

After graduating from the Feinberg School of Medicine at Northwestern University in Chicago, Dr. Belani came to St. Louis for her residency in internal medicine in 1999, after she and her then fiancé, Jay Belani, both matched at Barnes-Jewish Hospital for residencies (he's a urologist). "What drew me to nephrology were the initial experiences I had with the attendings, who had passion and drive for renal physiology and were the 'thinking' internal medicine experts."

She still can recall many cases and experiences in the Division of Nephrology, even fifteen years after she moved from St. Louis to San Rafael, Calif. "One of my fondest memories there was on late night rounds with Aubrey Morrison, Will Ross and Stanley Misler," she says with a laugh. "We would have 30 or 40 hospital patients and then, between 7 and 8 p.m., they would all sit down with a marker and dry erase board and go through each patient in excruciating detail. It actually was quite fun as well as educational!"

And recalling her time with Daniel Brennan in transplant nephrology she says, "The amount of expertise we developed in post-transplant care was so profound that I only realized later how unique and special it was. I think that's why I value that education to such an extent now. It taught me the many roles of a physician — caregiver, researcher, and as leader in advocating for the very best in patient care."

Being part of an integrated healthcare system allows Dr. Belani to use large-scale data that can then help physicians identify patients at high risk for diseases. "Once we see those who have the highest risk, we can educate the patients and primary physicians and implement interventions to slow down or minimize progression of disease."

When she's not at the office, Dr. Belani and her husband, who have two children ages 13 and 15, spend much of their leisure time being active, whether it's hiking, skiing, or being on the water near their home.





Sharina Belani, MD, and her family on one of their many outdoor adventures.

Program Spotlight

Demand is High for Interventional Nephrology Services

After opening a new interventional nephrology clinic last spring in west St. Louis County, the Division has seen rapid growth in the demand for services.

"We've seen 300 percent growth over the first year," says James Davis, MD, FACP, FASN, who oversees the clinic. "It's been amazing to see the referrals grow so quickly."

The clinic is a joint partnership with St. Luke's Vascular Access Center. Davis focuses specifically on fistula and graft care. "We provide maturation assistance for immature AVF, angioplasty and thrombectomy of grafts and fistula and all manner of dialysis catheter care, including

insertion and exchange," he says. "We also offer accessory vein obliteration to assist with maturation and cannulation."

Davis, who has been an interventional nephrology specialist for more than 15 years both here and in Ohio, says there are several reasons for the demand for services. First, he says, former WU nephrology fellow Steve Bander, MD, who heads the St. Luke's Vascular Access Center, has been very supportive of Davis joining the team, which offers 24/7 treatment for patients with central venous catheter complications. "I have the flexibility to see patients every day and get them cared for quickly," Davis explains. He also points out that the Division has ensured that physicians

are aware of the center as a "first call" option when access issues arise.



James Davis, MD

New Renal Services Clinic for Veterans

The Division of Nephrology has started a new renal diseases clinic at the Veterans Affairs outpatient facility in north St. Louis county. Manasa Metireddy, MD, who is now part-time faculty with the VA, will head the new clinic. Veterans with various conditions such as chronic kidney disease,

kidney stones, glomerulonephritis as well as hypertension, will be seen in the clinic.

"Our hope is that this clinic will decrease the drive time and wait times for veterans who live in north county and who need these critical services," she says.

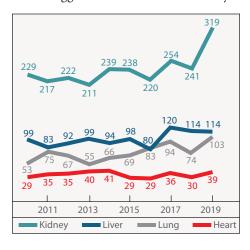
Metireddy, who joined the Division in fall 2018, is part of the Division's community-based faculty practice. She and James Davis, MD, oversee the Washington

University dialysis unit in north county as well as offer inpatient renal services at Christian Hospital and Barnes-Jewish West County Hospital.

"Both inpatient and outpatient renal services have experienced growth within the past year and we anticipate the new veterans' clinic to do the same," Metireddy says. "It's all about placing services closer to patients' home and making access more convenient."

Another Record Year for Kidney Transplants!

With the 8th largest organ transplant center in the nation, the Washington University and Barnes-Jewish Hospital Transplant Center logged a record number of kidney



transplants last year — 319 transplants! That's an increase from 241 transplants performed in 2018.

"The jump in the number of transplants is due primarily to increased referrals as a result of strong collaborations with the referring nephrologoists, extensive outreach efforts, and the increased utilization of kidneys donated after cardiac death (DCD)," Says Tarek Alhamad, MD, medical director of Kidney and Combined Kidney/ Pancreas Transplantation.

Transplant nephrologist Haris Murad, MD, who joined the team in mid-2019, also notes that better patient education efforts resulted in an increase in the number of patients undergoing living donor transplants. "This was achieved through more robust counseling of patients who are seen in the pre-transplant clinics as well as educational

talks for those who are already waiting for an organ," he says. "When patients are told that a living donor transplant will give them a better quality organ while also preventing them from waiting several years for a kidney, many of them reach out to more relatives and friends in the quest for a donor."

Last year, the team performed 73 living transplants, up from 55 the previous year. Living donor evaluations also increased, from 356 in 2018 to 408 last year. Murad notes, "While our transplant numbers are increasing, the fact that close to half a million patients are on dialysis means we still have a lot more to achieve in terms of finding kidney donations. We have almost 800 patients still on our own waiting list right now and receive more than 1,700 referrals annually to our program."

Research Highlights

2020 Translational Innovation Grant Awarded

The Division of Nephrology's 2020 Translational Innovation grant has been awarded to Sanjay Jain, MD, PhD, and Tingting Li, MD, MSCI. This year's project will focus on developing methods for single nucleus transcriptomic studies on archived diagnostic frozen kidney biopsy tissue from patients with pauci immune glomerulonephritis (PIGN).

The \$50,000 grant program has been offered for the past five years to stimulate innovative, translational collaborations between a basic scientist and a clinician in the Division. Jain and Li note that PIGN is a hallmark of ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis (AAV) and is the

most common cause of crescentic GN in the adults.

"Using single nucleus transcriptomics, we will redefine PIGN at a molecular level, provide novel insights into pathogenesis and transformation of cellular phenotypes and uncover diagnostic and prognostic biomarkers," says Jain. "We hope that our methods of interrogating archived frozen biopsy using single cell technologies, which is paradigm-shifting in the field, will be broadly applicable to other diseases and tissues."

Adds Li, "Despite advances in treatment, a significant proportion of PIGN patients do not achieve complete or sustained remission and many remain at high risk for end-stage renal disease and death.





Sanjay Jain, MD, PhD

Tingting Li, MD, MSCI

To date, there are no reliable biomarkers that predict therapy response, relapse, or clinical outcomes for these patients. If our proof-of-concept studies are successful, it will provide critical insights into the immunopathogenesis of PIGN and could pave the way for translational studies that will have broad implications in diagnosis, outcome prediction, and targeted therapies for this disease."

\$3 Million NIH Grant Awarded for Cilia Research

A four-year, \$3.14 million RO1 renewal grant from the National Heart, Lung, and Blood Institute (NHLBI) grant has been awarded to three prominent Washington University researchers to study the "Regulation of Motile Cilia Assembly in Lung Disease."

Principal investigators include Moe Mahjoub, PhD, Assistant Professor of Medicine (Division of Nephrology), Cell Biology and Physiology; Susan Dutcher, PhD, Professor of Genetics, Cell Biology and Physiology; and Steven Brody, MD, the Dorothy R. and Hubert C. Moog Professor of Pulmonary Medicine. The three, all collaborators in the Washington University Cilia Group, collectively and individually research the mechanisms and causes of ciliopathies, which include polycystic kidney disease

and genetic lung diseases such as primary ciliary dyskinesis (PCD), among others.

The current research effort focuses on how genetic defects in cilia function result in PCD, lung infection and the development of chronic lung disease. Researchers have found that these gene mutations result in defective production, transport, or proper placement



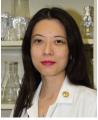
of ciliary motors along the ciliary axoneme. How this occurs, however, is not understood, impeding the development of therapeutic strategies. The researchers are investigating how ciliary motor components are directed from the cell body into the cilia and then to specific sites along the ciliary axoneme. "Just as movement through a city requires multiple modes of transportation, certain proteins must be moved from the cytoplasm to the basal bodies and into cilia using defined vehicles and routes," say the investigators. "We are expanding our previous research to define how these proteins are delivered to their appropriate addresses within each cilium and how disease-causing mutations impact these key trafficking steps."

Cilia research Pls include Steven Brody, MD, Susan Dutcher, PhD, and Moe MahJoub, PhD.

Department of Defense Grant Awarded to Chen

Ying "Maggie" Chen, MD, PhD, has been awarded a \$1.8 million grant from the U.S. Department of Defense for her study, "Development of Novel Podocyte Endoplasmic Reticulum (ER) Calcium Stabilizers to Treat

Focal Segmental Glomerulosclerosis (FSGS). FSGS is the most common primary glomerulopathy leading to renal failure and disproportionately affects African-Americans, a highly represented population among military personnel and veterans.



Maggie Chen, MD, PhD

The ultimate goal, says Chen, is to develop a new class of drugs — podocyte ER calcium stabilizers — to treat FSGS. While it is known that podocyte ER stress plays an important role in the pathogenesis of FSGS, there is no treatment option currently available that targets podocyte ER.

Faculty News and Awards

Vijayan Inducted Into Alpha Omega Alpha



Anitha Vijayan, MD, professor of medicine in the Division of Nephrology, has been elected to Alpha Omega Alpha, the national

medical honor society. "AOA stands for excellence in academic scholarship, leadership and professionalism," Vijayan says. "I am passionate about providing exemplary patient care and educating the next generation of physicians, and I am privileged to be doing both at an outstanding institution. I am truly honored that my work is recognized in this way." Vijayan was nominated for the honor by Division Chief Benjamin Humphreys, MD, PhD, and Victoria Fraser, MD, chair of Washington University's Department of Medicine.

Steven Funk, PhD Joins Division



Instructor of medicine Steven Funk, PhD, is the newest faculty member in the Division. Funk previously served as a post-doctoral

research fellow in the laboratory of Jeffrey Miner, PhD. He earned his doctoral degree in cell biology and anatomy from Louisiana State University Health Sciences Center in

Shreveport, La. While working in Miner's lab, Funk helped to develop a non-invasive, novel method that uses hair follicles to diagnose X-linked Alport syndrome. The inherited disease is characterized by a progressive loss in kidney function and hearing as well as eye abnormalities.

Delos Santos Chairs AST Conflicts of Interest Committee



Rowena Delos Santos, MD, takes over as chair of the Conflicts of Interest (COI) Committee of the American Society of Transplantation

(AST) in June 2020. Delos Santos, who is director of the Division's Transplant Nephrology Fellowship, has served as co-chair of the COI committee since last year. The committee reviews all disclosures of potential conflicts of interest made by AST speakers, moderators and planning committee members.

Lifetime Achievement Award in **Nephrology Nursing**



Lisa Koester-Wiedemann, ANP, CNN-NP, was awarded the Barbara Prowant Lifetime Achievement Award in Nephrology

Nursing. Koester-Wiedemann is responsible for clinical coverage of in-center hemodialysis, home dialysis, and the chronic kidney disease patient population. The award, given during the 40th Annual Dialysis Conference this past February, is named in honor of Barbara Prowant, a renowned nephrology nurse and founder of the conference, which was established in 1981 as the world's largest multidisciplinary conference on dialysis.

President-Elect Miner Chairs ASMB Biennial Meeting in St. Louis

Make plans to come to St. Louis for the 2020 biennial meeting of the American Society for Matrix Biology (ASMB). Chair of the meeting will be Jeffrey Miner, PhD, FASN, who also will become president of the organization in 2021. "ASMB's 2020 meeting, "The Matrix in Focus: Matrix, Cells, and Interactions in Health, Disease, Aging, and Regeneration", will bring together matrix biologists from around the world to share knowledge and foster collaborations regarding extracellular matrix biology in order to improve human health," notes Miner. "Defects in the extracellular matrix can impact all tissues. This is especially true in the kidney, where genetic defects in collagen IV cause Alport syndrome, and dysregulated matrix production causes renal fibrosis." The organization anticipates more than 350 extracellular matrix biologists to attend the meeting, which will be held at the Hyatt Regency, St. Louis Arch.

Tackling Readmission Rates

Frank O'Brien, MD, received a two-year, \$240,000 grant from The Foundation for Barnes-Jewish Hospital to create a personalized transitional care protocol for dialysis patients discharged from the hospital to home. Average 30-day readmission rates for end-stage renal disease patients nationwide is 39 percent, compared to 15 percent for all hospitalized patients in the general Medicare population. O'Brien will look at the high 30-day readmission rates of dialysis patients here and work to enhance communications, follow-up care and patient education through the use of a dedicated transitional care team comprising a physician, nurse coordinator and social worker.



Frank O'Brien, MD

Washington University in St. Louis

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Tennis, Anyone?

Vikas Dharnidharka, MD, Chief of Pediatric Nephrology, can serve up a fun time, for sure! Last summer, he won two 4th place ribbons in his age category at the National Senior Games Table Tennis Tournament in Albuquerque, New Mexico.

"There are a lot of ways to relieve stress," he says. "Table tennis I'm good at. Games involve skill, and there is physical exercise. It takes you away and gives you a life outside of work, too. I like all of that. It's fun!"

Dharnidharka placed 4th in both the men's double and mixed double matches at the National Games. He is garnering quite the streak — Last year, he won three medals at St. Louis Senior Olympics Table Tennis Tournament: a gold medal in mixed doubles, a silver in men's doubles, and a bronze in singles. At the same tournament in 2018, he won a gold medal in the singles match and a silver medal in men's doubles. Now, his wins in 2019 may qualify him for the 2021 National Games.

Dharnidharka, who also is a member of the Board of Directors of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) organization, grew up playing table tennis in India. "It was so crowded there, that most indoor sports were easier to play than outdoor sports. You

needed less space." He re-discovered the sport after coming to St. Louis and began playing weekly in the St. Louis Table Tennis League. "When I discovered the league here, I was able to get better because I'm playing against people of all ages and all levels, so my game really improved."



Vikas Dharnidharka, MD, at the National Senior Games Table Tennis Tournament.