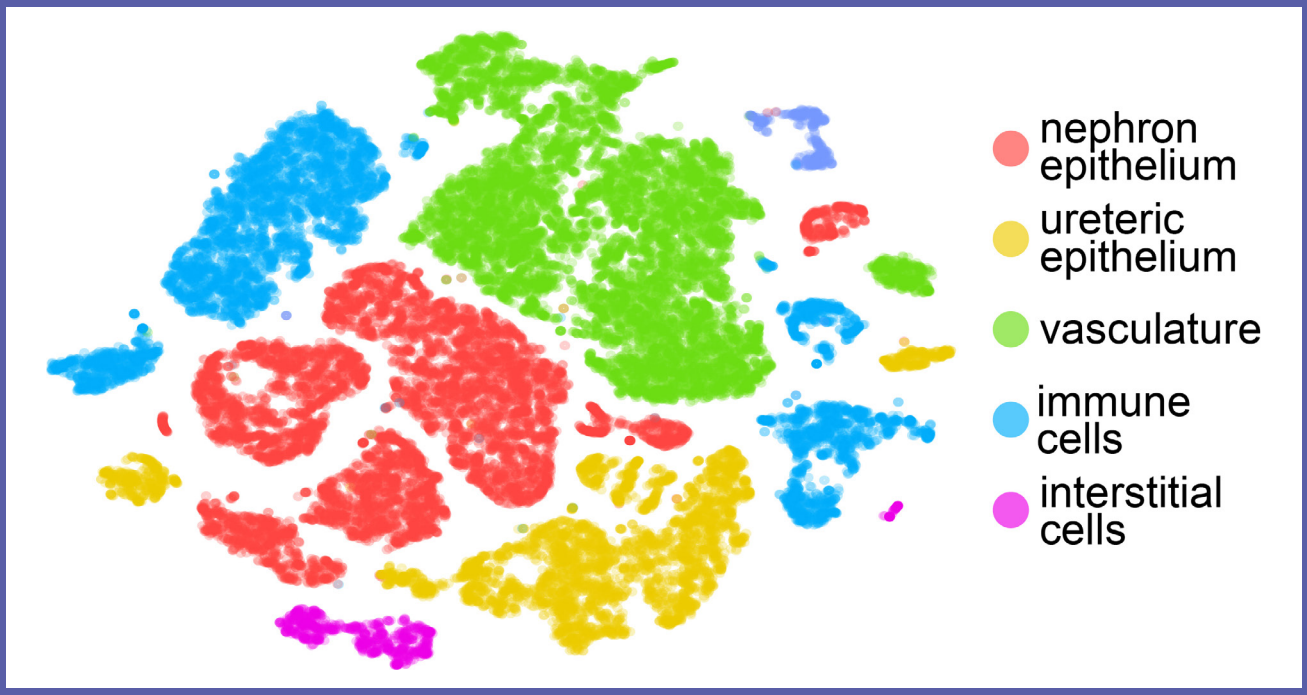

As described in this chapter, researchers have reported significant new findings about kidney development and three-dimensional structure in mice. Normal, healthy kidneys filter waste products from blood. Millions of people have kidney disease and kidney failure, and a better understanding of the cellular functions and development of the kidneys is essential to developing approaches to prevent, reverse, or repair injured and diseased kidneys. The investigators used single-cell analysis combined with cell-fate mapping studies, in which early-stage cells are biologically labeled such that the specialized cells that derive from them also contain the label. These cutting-edge techniques enabled the investigators to gain new insights into how nephrons (filtering units of the kidney) differ in the outer versus middle parts of the kidney, the cellular origins of different structures and junction points of nephrons, and intriguing sex differences in nephron gene expression (*i.e.*, whether a gene is turned on or off). With this wealth of novel information, the researchers have constructed a Web-searchable, annotated anatomical database of the adult mouse kidney for use by the scientific community. An example of the kinds of data available in the database is shown and highlights the diversity of cells and organizational structures residing within the kidney. Furthermore, users can analyze the data set in various ways, for example, to learn about different genes, obtain a graphical representation of the anatomical location of a gene of interest within the kidney, and distinguish gene expression patterns by cell types in nephrons.

Image provided by Dr. Andrew P. McMahon, Keck School of Medicine of the University of Southern California. Reprinted from Dev Cell; Vol 51; Ransick A, Lindström NO, Liu J,...McMahon AP; Single-cell profiling reveals sex, lineage, and regional diversity in the mouse kidney; Pages 399-413.e7; Copyright 2019, with permission from Elsevier.

Kidney, Urologic, and Hematologic Diseases

Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the United States. They affect millions of Americans, and their impact is felt across the lifespan. To improve our understanding of the causes of these diseases, and to identify potential new prevention and treatment strategies, the NIDDK supports basic and clinical research studies of the kidney and urinary tract and of the blood and blood-forming organs. The overall goal of the NIDDK's research programs is to improve the health of people who have or are at risk for kidney, urologic, and hematologic (blood) diseases.

Normal, healthy kidneys filter about 200 quarts of blood each day, generating about 2 quarts of excess fluid, salts, and waste products that are excreted as urine. Loss of function of these organs, either for a short period of time or as a consequence of a gradual, long-term decline in kidney function, is a life-threatening condition.

It has been estimated that 37 million American adults have impaired kidney function—also called chronic kidney disease (CKD).[1] CKD has two main causes: high blood pressure and diabetes. The increases in obesity and type 2 diabetes in the United States in recent years—especially among children and adolescents—have grave implications for the Nation's health, as young people with these conditions are likely to face serious health complications at an earlier age than people who historically have developed these conditions later in life.

One feature common to kidney diseases arising from varying causes is the deposition of fibrotic scar tissue in the kidney. Research supported by the NIDDK has enhanced our understanding of the origin of this scar tissue, how it can impair kidney function, and how it might be prevented or treated. CKD, especially if undetected, can progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). People with ESRD require dialysis or a kidney transplant to live. In 2018, over 783,000 patients received treatment for ESRD: over 554,000 received either hemodialysis or peritoneal dialysis, and over 229,000 were living with a kidney transplant.[2] Racial and ethnic minority populations in the United States, particularly African Americans, Hispanic and Latino Americans, and American Indians and Alaska Natives, bear a disproportionate burden of CKD and ESRD. Compared to Whites, ESRD prevalence in 2018 was about 3.4 times greater in African Americans, 1.9 times greater in American Indians or Alaska Natives, and 1.3 times greater in Asians.[2] Compared to all non-Hispanics, Hispanics had 1.5 times the risk for kidney failure.[2] In recent years, scientists supported by the NIDDK have uncovered important genetic clues that may play a role in some of the health disparities related to kidney disease susceptibility and progression in minority populations.

The Institute supports a significant body of research aimed at understanding the biology underlying CKD and developing treatment strategies. The NIDDK's chronic renal diseases program supports basic and clinical research on kidney development and disease, including the causes of kidney disease, the underlying mechanisms leading to progression of kidney disease to ESRD, and the identification

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[1] *Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2019.*

[2] *United States Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.*

and testing of possible strategies to prevent development or halt progression of kidney disease. In addition to research on kidney disease related to diabetes and high blood pressure, the NIDDK also supports studies of inherited diseases, such as polycystic kidney disease, congenital kidney disorders, and focal segmental glomerulosclerosis; and immune-related kidney diseases, such as IgA nephropathy and hemolytic uremic syndrome. The CKD Biomarkers Consortium (CKD BioCon) promotes the discovery and validation of novel biomarkers for CKD initiation, progression, and development of complications. A more complete understanding of biomarkers could allow physicians to detect kidney disease earlier and perhaps identify people at greater risk of progression, allowing them to tailor treatments to a specific individual. The Kidney Precision Medicine Project is obtaining and evaluating human kidney biopsies from participants with acute kidney injury (AKI) or CKD for the purpose of creating a kidney tissue atlas, defining disease subgroups, and identifying critical cells, pathways, and targets for novel therapies.

Urologic diseases affect people of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life. The NIDDK's urology research program supports basic and clinical research on the normal and abnormal development, structure, function, and injury repair of the genitourinary tract. Areas of interest include the causes of and treatments for urologic diseases and disorders, such as benign prostatic hyperplasia, urinary incontinence, urinary tract infections, and urinary stone disease. To spur research in urinary stone disease, the Urinary Stone Disease Research Network (USDRN) is: (1) conducting a randomized clinical trial to investigate the impact of increased fluid intake and increased urine output on the rate of recurrence of urinary stones in adults and children; (2) conducting clinical research to understand and mitigate ureteral stent-related pain and symptoms; and (3) providing data and collecting biological samples from the studies to create a resource for future researchers.

Other disorders of the genitourinary tract, such as interstitial cystitis/bladder pain syndrome (IC/BPS)—also known as IC/painful bladder syndrome (PBS)—in women and men and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men, are also important research topics of the NIDDK's urology program.

IC/BPS is a debilitating, chronic, and painful urologic disorder. Based on a recent large, national interview survey, it is estimated that among U.S. women 18 years or older, 3.3 million (2.7 percent) have pelvic pain and other symptoms, such as urinary urgency or frequency, that are associated with IC/BPS.[3] Using a community-based epidemiologic survey, researchers have estimated that among U.S. men ages 30 to 79 years old, 1.6 million (1.3 percent) have persistent urologic symptoms, such as pain with bladder filling and/or pain relieved by bladder emptying, that are associated with BPS.[4]

NIDDK-supported basic and clinical research on IC/BPS and on CP/CPPS is focused on elucidating the causes of these conditions, identifying important subsets of patients to aid diagnostic stratification, and improving treatment and interventions. One example of an ongoing study is the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, which supports research designed to uncover the underlying causes of IC/BPS and CP/CPPS and to characterize the disease profiles in affected persons.

Based upon national public health surveys conducted over several years, it is estimated that about 54 percent of women (20 years and older) report urinary incontinence in the past 12 months. Urinary incontinence was self-reported by approximately 15 percent of men surveyed.[5] Many suffer in silence due to embarrassment and lack of knowledge about treatment options available. NIDDK-supported studies over the past several years have helped to advance knowledge about the efficacy of surgical treatment of urinary incontinence, as well as to provide new insights into non-surgical alternatives. As researchers continue to investigate treatment options, an equally important challenge is to identify and understand the important subgroups of people with lower urinary tract symptoms (LUTS) through improved measurement of patient experiences of LUTS in men and women. To address

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[3] Berry SH, et al. J Urol 186: 540-544, 2011.

[4] Link CL, et al. J Urol 180: 599-606, 2008.

[5] Urological Diseases in America, 2018 Addendum. NIDDK, NIH Publication Number 12-7865, 2018.

this challenge, the NIDDK supports the multi-site Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN). The NIDDK is also leading new efforts to explore whether it may be possible to prevent symptom onset and/or progression, thereby improving health. The NIDDK, in conjunction with the National Institute on Aging, the NIH Office of Research on Women's Health, and the NIH Office of Behavioral and Social Sciences Research, established the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium to develop the evidence base for normal or healthy bladder function and to identify behavioral and other risk factors for conditions associated with lower urinary tract symptoms in women.

The NIDDK's hematology research program uses a broad approach to enhance understanding of the normal and abnormal function of blood cells and the blood-forming system. Research efforts include studies of a number of blood diseases, including sickle cell disease, the thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, thrombocytopenia, and the anemia of inflammation and of chronic diseases. To promote high-impact basic or pre-clinical research, the Institute supports the Stimulating Hematology Investigation: New Endeavors (SHINE) program and includes the following current research topic areas: regulation of blood (hematopoietic) stem cells, factors that play a role in the development of different types of blood cells, and red blood cell maturation. The Institute's SHINE II program seeks to further catalyze research in basic or pre-clinical, proof of principle research projects that are tightly focused and directed at validating novel concepts and approaches that promise to open up new pathways for discovery in benign hematology research. The NIDDK is also keenly interested in the basic biology of adult hematopoietic stem cells, which are used clinically in bone marrow transplants and may have broader application in gene therapy research.

CHRONIC KIDNEY DISEASE PROGRESSION IN CHILDREN

Identifying Children at Increased Risk of Chronic Kidney Disease Progression: A new study has described different trajectories of chronic kidney disease (CKD) progression in children that will aid in identifying those at high risk for progressive disease. The basic functional unit of the kidney is the nephron, which consists of various cells and structures that work together to filter waste products, remove excess fluid from the blood, and balance various body chemicals. Of these structures, the glomerulus is the fundamental filtering apparatus. A common kidney function measurement called the glomerular filtration rate (GFR) is an estimate of blood filtered per minute by all the nephrons within the kidneys. The ability to predict CKD progression, as measured by declining GFR, is a major challenge for nephrology (the medical specialty focused on the kidneys).

Using publicly available Chronic Kidney Disease in Children (CKiD) study data through the NIDDK Central Repository, researchers employed a statistical modeling approach to establish GFR trajectories (*i.e.*, changes in kidney function over time) in female and male participants with glomerular and non-glomerular diseases. CKiD is a multi-center study of children ages 1 to 16 years with mildly to moderately impaired kidney function. The CKiD researchers are monitoring the health of these children over time in several areas, including determining the risk factors for decline in kidney function, and defining how progressive decline in kidney function affects biomarkers of risk factors for cardiovascular disease, evaluating several brain functions (*e.g.*, attention, perception, memory, language, and behavior), and assessing growth failure and its associated morbidity. Using data from CKiD, this study found two distinct GFR trajectories for glomerular disease while four distinct GFR trajectories were reported for non-glomerular disease. Glomerular and non-glomerular diseases displayed very different GFR trajectories—among those with glomerular disease, a subset of female participants had a rapid GFR trajectory decline indicating rapid loss of kidney function, whereas no difference was observed between sexes in those with non-glomerular diseases.

This valuable new information from a subset of girls with rapidly progressing glomerular disease will enable clinicians to better prepare their patients and their families for kidney transplantation or dialysis. Furthermore, girls have lower access to kidney transplantation in the United States than boys, and this study could help address this disparity.

Bonnéric S, Karadkhele G, Couchoud C, Patzer RE, Greenbaum LA, and Hogan J. Sex and glomerular filtration rate trajectories in children. Clin J Am Soc Nephrol 15: 320-329, 2020.

NEW INSIGHTS INTO KIDNEY DEVELOPMENT

New Kidney Mapping Could Lead to Health Gold: Through studies in mice, researchers have gained fundamental new insights into kidney development and organization and how they differ between males and females—all of which could aid research efforts to battle human kidney diseases. Human and animal kidneys are highly complex. Within each kidney, myriad essential structural and functional units, called nephrons, are arranged radially in an interconnected pattern resembling a dense tree crown. Together, nephrons carry out the kidneys' primary function of filtering the blood to remove wastes, as well as other important activities. A better understanding of the cellular functions and development of nephrons—including sex differences that might underlie observed differences between women and men in protection from kidney injury—is key to finding ways to reverse, avoid, or repair kidney injuries and diseases.

In a major advance, researchers used a painstaking method called single-cell RNA sequencing to identify genes that are expressed (turned on or off) in adult male and female mouse kidney cells. To organize the results, they divvied each kidney into three zones corresponding to its outer, middle, and innermost anatomical regions prior to extracting cells, and assigned representative cells from each zone into "clusters" based upon gene expression patterns. They then combined those results with the results of imaging studies that allowed them to visualize, trace, and compare the development and localization of different mouse kidney tissues and structures over time from the embryonic stage to maturity. Together, these experiments yielded a wealth of information, such as details on how nephrons differ in the outer versus middle parts of the kidney, the cellular origins of different structures and junction points of nephrons, and intriguing sex differences in nephron gene expression that provide new targets for study. For example, evidence suggests that female mice and humans are resistant to a type of kidney injury that primarily affects a section of the nephron called the proximal tubule. The researchers found that the expression of genes involved in transport of small molecules and metabolism of drugs, cholesterol, and hormones—all functions of the proximal tubule—differed between female and male mice. Interestingly, in a second recent study, another team of researchers also found differences in gene expression between female and male mice when they examined the same section of the nephron post-injury, further bolstering the importance of this region—and these genes—as study targets in understanding kidney disease and kidney protection.

Researchers from the first study have used their results to generate a Web-searchable, annotated anatomical database for use by the scientific community. Although there are limitations on some of the data—for example, some kidney cell types were underrepresented in the study because they did not survive the experimental procedures—these results from mice can serve as a guidepost in similar mapping of human kidney. This research also points to potential explanations for both general vulnerabilities and sex-specific protective factors in kidney injury and ultimately a better understanding of kidney diseases and kidney failure—and thus new ideas for therapies.

Ransick A, Lindström NO, Liu J,...McMahon AP. Single-cell profiling reveals sex, lineage, and regional diversity in the mouse kidney. Dev Cell 51: 399-413.e7, 2019.

Wu H, Lai C-F, Chang-Panesso M, and Humphreys BD. Proximal tubule translational profiling during kidney fibrosis reveals proinflammatory and long noncoding RNA expression patterns with sexual dimorphism. J Am Soc Nephrol 31: 23-38, 2020.

Unraveling the Molecular Nature of Blood Vessel Specialization in the Kidney: Scientists have identified critical sets of genes turned on in individual cells within discrete, specialized zones of blood vessels in the mouse kidney during development and adulthood—findings that could have important implications for developing artificial kidney technologies. The activities of nephrons—the essential structural and functional units of the kidney—would be impossible without the blood vessels that intertwine with them. These blood vessels, or vasculature, are not uniform, but instead become specialized according to their position within a nephron to help carry out the precise function of each nephron segment or substructure (*e.g.*, retention of sugars, reabsorbtion of water to help maintain fluid balance in the body). This vascular specialization by zone is essential for proper kidney formation and function, but the molecular pathways driving this specialization

have been unknown, hindering the development of promising technologies such as artificial kidneys. A research team recently identified critical molecules regulating this process in mice.

Using sophisticated cell-sorting techniques, the scientists isolated individual blood vessel cells, called endothelial cells (ECs), from the kidneys of developing mouse embryos, as well as from postnatal and adult male mice, and identified all the genes that were turned on in those individual cells. They also compared the genes turned on in ECs in bulk from kidneys to those of the lung, liver, and heart, to identify those with activity specific to kidneys. Comparisons of the kidney-specific EC gene "molecular profiles" revealed several distinct clusters of genes that correspond to the different structures and functional regions within the nephron; there were also significant differences between mouse embryonic and adult kidneys. Further examining ECs, the scientists found that different genes were active in different vascular zones, such as genes involved in regulating the absorption of specific molecules, providing developmental instructions to neighboring cells, or turning other critical genes on or off. The researchers then tested the importance of the gene *Tbx3*, which they had found to be particularly active in a critical segment of the nephron called the glomerulus. They genetically deleted *Tbx3* specifically in glomerulus ECs in male mice and found defects in the structure of the glomerulus that affected blood pressure and led to aberrant filtration of molecules from the blood. With other experiments, these results indicate that *Tbx3* governs genes important to glomerular blood vessel development and function. Importantly, the scientists also tested the gene in cultured human endothelial cells and found that human *TBX3* likely has a similar function as the mouse gene.

The distinct kidney EC molecular profiles identified in this study shed critical light on the processes that create and maintain discrete vascular zones in the nephron. These findings could provide a foundation to help accelerate the engineering of functional artificial kidneys.

Barry DM, McMillan EA, Kunar B,...Rafii S. Molecular determinants of nephron vascular specialization in the kidney. Nat Commun 10: 5705, 2019.

RESEARCH ON LOWER URINARY TRACT SYMPTOMS

Symptom-based Clustering in Men with Lower Urinary Tract Symptoms: New research has employed an algorithm to identify novel subgroups of men with different lower urinary tract symptoms (LUTS) based on detailed symptom information—results that could help in understanding and treating LUTS in the future. LUTS are highly prevalent in both males and females, but many people who seek help from health care providers for LUTS experience neither total nor permanent resolution of their symptoms with current management approaches. One of the barriers to improving diagnosis and management of LUTS is incomplete knowledge and imprecise classification of subtypes of LUTS and their associated causes. There are a wide variety of LUTS that people can experience, such as problems with emptying (voiding) urine from the bladder, which may be caused by problems in the urinary tract or may originate elsewhere in the body. Even people with similar symptoms may have different underlying urinary tract conditions.

A study conducted through the NIDDK-supported Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) sought to overcome some of the barriers to diagnosis and management. Using a consensus clustering algorithm—a novel approach that did not rely on conventional clinical definitions to group patients—they analyzed responses to self-administered questionnaires to identify distinct symptom signatures in 503 care-seeking men with LUTS, the majority of whom were Caucasian with an approximate average age of 61. Four separate symptom clusters (CL1-4) were identified among participants, with the following characteristics. The 166 participants in CL-1 had predominant urinary symptoms of hesitancy (difficulty starting or maintaining urine stream), straining, weak stream, incomplete bladder emptying, frequency, and nocturia (waking from sleep to urinate)—a pattern suggestive of bladder outlet obstruction. The 93 participants in CL-2 mainly had symptoms of post-void dribbling and post-void urinary incontinence. The 114 participants in CL-3 had predominant symptoms of urinary frequency and nocturia without incontinence. The 130 participants in CL-4 had symptoms of severe urinary frequency, urgency, and urgency incontinence.

Future research may examine these four symptom clusters in the context of biomarkers, and how the brain and/or nervous system may be influencing bladder function. For example, neuroimaging may identify differences in brain structure and function as it relates to bladder control, and sensory testing could explore whether differences exist in nervous system responses to auditory (hearing) and pain stimuli. Findings from such studies could provide insight into the complexities of male LUTS, while validation studies can help to determine if the groupings are helpful to clinical diagnosis and management of LUTS across men in the U.S. population. Furthermore, the phenotypic clusters identified by the LURN consortium provide a foundation in which to test the effectiveness of treatments.

Liu G, Andreev VP, Helmuth ME,...Kirkali Z; LURN Study Group. Symptom based clustering of men in the LURN Observational Cohort Study. J Urol 202: 1230-1239, 2019.

IMMUNE SYSTEM RESPONSES TO URINARY TRACT INFECTIONS

Immune System Response Could be Undermining Ability To Fight Urinary Tract Infections: New findings in mice about immune system responses to urinary tract infections (UTIs) could help explain the high rates of UTI recurrence in humans and suggest novel ways to treat them. UTIs are very common, especially in women, many of whom suffer repeated infections with symptoms such as painful urination and a frequent or intense urge to urinate. The most common cause of UTIs is a bacterium normally found in the human intestines, called *Escherichia coli* (*E. coli*); uropathogenic *E. coli*, or UPEC, are those able to infect the urinary tract and sometimes the kidneys. While UTIs can be treated with antibiotics, the threat of increasing bacterial antibiotic resistance is driving research to identify new therapeutic approaches.

To gain insights that could lead to potential therapeutic targets, researchers are examining not only bacterial factors that enhance UPEC infectivity, but also factors and responses in human and animal model hosts that can either help or hamstring the ability to ward off UTI-causing microbes. For example, one way both humans and mice respond to UTIs is to shed infected cells lining the inside of the bladder—an early, innate response to UTIs that is mediated by certain immune system cells residing in the bladder. Though drastic, as it damages the bladder lining, cell shedding reduces infection in the bladder wall. Simultaneously, other cells of the immune system begin to organize so-called adaptive responses to the invading microbes that are supposed to help fight the bladder infection in a more targeted fashion, such as through developing antibodies. However, humans and mice appear not to develop a robust antibody response against UPEC that would help kill residual bacteria and protect against subsequent infections. Instead, researchers have now uncovered evidence in mice strongly suggesting that, rather than being balanced, the adaptive immune response to bladder infection by UPEC is highly biased toward aiding repair of the bladder lining and inhibits responses that would clear UPEC. The researchers used mouse models deficient in different adaptive immune responses and/or genetically engineered to enable detection of cells involved in these responses. Studying these mice, the scientists were able to identify distinct subsets of immune system cells responsible for initiating and executing this biased response and the steps involved in establishing it in the bladder. Moreover, when the scientists exposed mice to multiple rounds of UPEC infection, they observed that the bias toward tissue repair was reinforced over time and, in fact, led to a thickening of the bladder lining that ultimately reduced mouse bladder capacity.

Repair of the bladder lining is critical for protecting underlying cells from noxious waste molecules present in urine—a unique challenge posed by the innate response to UTIs. However, the high bias toward repair and consequent inhibition of a robust companion antibody response could be contributing not only to recurrent infection but also to development of bladder dysfunction, such as urinary urgency or incontinence. This possible connection can now be explored, along with methods to reestablish balance in the host response to UTIs that could improve outcomes and prevent recurrence.

Wu J, Hayes BW, Phoenix C,...Abraham SN. A highly polarized T_H2 bladder response to infection promotes epithelial repair at the expense of preventing new infections. Nat Immunol 21: 671-683, 2020.

PROGRESS TOWARD TREATING URINARY STONES

Moving Objects with Ultrasound Beams—Potential Application to Urinary Stone Disease: Researchers have developed a noninvasive technology using ultrasound beams to lift and reposition an object in a living animal—an advance that could potentially be used to treat people with urinary stone disease. Urinary stones (also referred to as kidney stones) are one of the most common disorders of the urinary tract. Smaller stones may pass with little or no pain, while larger stones may get stuck along the lower urinary tract and block the flow of urine, causing severe pain and/or bleeding. Current treatments for urinary stones, such as lithotripsy that breaks stones into smaller pieces, may leave behind residual stone fragments. Most fragments will pass on their own, but others may grow larger, cause pain, and may require the need for additional treatment.

Working to advance safe, effective, and more efficient ways to reposition and encourage the passage of urinary stones, researchers have developed a noninvasive strategy to essentially trap a stone in an ultrasound beam (*i.e.*, acoustic trapping). Trapped within this beam, the stone can be moved or repositioned by either moving the device that generates the ultrasound waves (*e.g.*, transducer) or electronically steering the ultrasound beam by altering the phase of the wave. The scientists first demonstrated that the ultrasound beam could trap, lift, and steer a 3-millimeter glass sphere under ideal conditions—in a water tank. They moved the sphere a total distance of 6 millimeters vertically and 6 millimeters horizontally. The researchers further reported that this noninvasive acoustic trapping approach successfully moved glass spheres in the urinary bladders of three female pigs. To accomplish this, a single 3-millimeter glass sphere was placed in the bladder of each anesthetized animal using a tube with a camera-equipped scope and a device carrying the glass sphere. The camera monitored the sphere movement and was used to evaluate changes to the bladder wall after each acoustic trapping manipulation. Importantly, the technology did not cause detectable injury to the animals' bladder wall.

This study demonstrates the ability to manipulate objects in the pig bladder using acoustic trapping, with potential application to treating urinary stones as well as other medical uses. Future research will be needed to evaluate the safety and effectiveness of this approach with respect to variations in shape, structure, and composition of urinary stones along the entirety of the urinary system, as well as to determine if it could be used in people. The technology associated with this translational work has been licensed to a small business.

Ghanem MA, Maxwell AD, Wang Y-N,...Bailey MR. Noninvasive acoustic manipulation of objects in a living body. Proc Natl Acad Sci USA 117: 16848-16855, 2020.

NEW INSIGHTS INTO BLOOD DISORDERS

Putting the "Brakes" on Adult Blood Stem Cell Proliferation: A recent study revealed a natural process that limits the ability of adult blood stem cells to proliferate (*i.e.*, divide to increase their numbers). The body's adult blood stem cells are able to replace blood cells damaged by disease, injury, or age. These cells can be found in either a state of quiescence or of proliferation. Previous research has shown that the transition from quiescence to the proliferative state requires the action of cellular structures called mitochondria, which take chemical energy from sugars and fats and convert it into fuel that is usable throughout the cell.

Recently, researchers reported that during proliferative growth the mitochondria of adult blood stem cells from both female and male mice accumulate defects that limit their ability to convert food energy into cellular fuel. When the cells return to their quiescent state, the resulting dysfunctional mitochondria are not repaired. Rather, their accumulation serves as a sort of record of each cell's replicative history. The researchers found that the mitochondrial defects result from loss of a protein called Drp1 that functions as part of the proliferative machinery. With each round of proliferative growth, Drp1 loss reduces the capacity of the blood stem cells to undergo future rounds of cell division. This phenomenon may effectively be an intrinsic "safety feature," limiting the cells' ability to proliferate excessively. Because such unchecked cell division can lead to cancer, understanding this process could one day lead to improved methods for prevention or treatment of cancers. In addition, this research may

help in the development of therapies that overcome the limits on adult blood stem cell proliferation in a selective fashion, allowing regeneration of critical blood cells that might otherwise be irrevocably lost through disease or injury.

Hinge A, He J, Bartram J,...Filippi M-D. Asymmetrically segregated mitochondria provide cellular memory of hematopoietic stem cell replicative history and drive HSC attrition. Cell Stem Cell 26: 420-430.e6, 2020.

Identification of Small Molecule Compound that Reverses Experimental Telomere-related Diseases: New research has shown that it may one day be possible to treat people with telomere-related diseases using small molecule compounds that restore telomerase levels to normal levels. Telomeres are protective segments of DNA at the ends of chromosomes, and telomerase is the protein responsible for maintaining the telomere-forming DNA sequences. Each time a cell divides, the telomeres become shorter because the telomerase is not very efficient at reading the DNA sequence all the way to the end. Eventually, the telomeres become so short that the cell can no longer divide—leading to telomere-related diseases (*e.g.*, blood diseases such as dyskeratosis congenita). Continued research over the past 30 years has illuminated many important molecules that regulate telomerase activity. Among them, the protein PARN (poly(A)-specific ribonuclease) has been shown to stabilize a component of telomerase, and thus the overall ability of telomerase to do its work. Notably, people with dyskeratosis congenita have been shown to have mutations in the *PARN* gene. Opposing the action of PARN is the protein PAPD5 (poly(A) polymerase associated domain-containing protein 5), which destabilizes telomerase activity. Strategies that target PAPD5 could potentially maintain the optimal function of telomerase by balancing PARN and PAPD5 activities.

In this study, researchers employed a high-throughput screening approach to test over 100,000 small molecules (chemical compounds), and they identified the small molecule BCH001 as capable of inhibiting PAPD5 at very low concentrations. Using cells from people with dyskeratosis congenita, BCH001 improved telomerase activity and elongated telomeres in cells with PARN mutations. To underscore the strategy of targeting PAPD5 to improve telomerase activity, the scientists tested another PAPD5 inhibitor, called RG7834, for its ability to restore telomerase activity. In this set of experiments, mice were transplanted with human blood stem cells that contained an experimentally mutated *PARN* gene. The researchers then gave the mice RG7834. Remarkably, oral administration of RG7834 reversed telomere shortening in *PARN*-deficient human blood cells compared to a control. This first-in-class therapeutic lead is an exciting new direction for potential treatment of telomere-related diseases.

Nagpal N, Wang J, Zeng J,...Agarwal S. Small-molecule PAPD5 inhibitors restore telomerase activity in patient stem cells. Cell Stem Cell 26: 896-909.e8, 2020.

Training Reimagined: Cultivating the Next Generation of Innovative and Collaborative KUH Researchers

The NIDDK's Division of Kidney, Urologic, and Hematologic Diseases (KUH) is reshaping and restructuring its Institutional Training Award program to cultivate a highly integrated cohort of trainees and early career investigators and to develop career development resources to accelerate research within KUH disease areas. This new "U2C/TL1" program, which replaces the NIDDK's previous "T32" grant mechanism, seeks to promote a true trainee community, with the overall goal of engaging, recruiting, preparing, and sustaining the next generation of kidney, urology, and hematology researchers. The first applications were submitted in the fall of 2020, and will be reviewed in 2021.

For decades, individual T32 training programs were typically small and focused on individual departments, at times resulting in multiple T32 programs at one institution with little research collaboration and no peer-to-peer networking among trainees across programs. However, despite large investments in KUH T32 programs, their trainees had a lower average rate of retention in research (as measured by the acquisition of subsequent research support) than trainees of the KUH "F"-series and "K"-series training programs. Some of the institutional T32 programs supported by KUH had markedly better outcomes than others, suggesting that there may be better practices and strategies that could be shared. To address these issues, the NIDDK convened the "KUH T32 Best Practices" meeting in May 2019, which provided a forum for sharing best practices and considering new approaches. Meeting attendees included T32 program directors, staff from the NIDDK and other NIH Institutes, and importantly past and present trainees. The group determined that in order to produce a diverse, modern workforce of researchers in fields relevant to KUH disease areas, a revitalized training program must:

- recruit talented individuals from diverse backgrounds;
- provide an environment to optimize trainees' ability to generate new knowledge;
- develop tailored and structured educational experiences;
- promote team and interdisciplinary science; and
- provide structured training in professional development, leadership, and mentorship.

Based on discussions, two clear themes emerged: (1) to support interdisciplinary collaborations, institutions need to create training programs that span multiple medical and graduate school departments; and (2) training experiences must be better structured to emphasize needed professional development in areas such as grant writing, presentation skills, and entrepreneurship. The new U2C/TL1 Institutional Network Award program was developed with these requirements and central themes in mind. Compared to traditional T32 programs, this new program will have fewer but larger Institutional Network Awards designed to cultivate the people and resources needed to propel KUH training and research.

The new U2C/TL1 programs will provide an environment designed to optimize the ability of trainees to conduct rigorous, ethical research to generate new knowledge, apply interdisciplinary approaches to research questions, and utilize principles of team science to further their leadership and problem-solving skills. Programs will also support the development of a peer-to-peer network and provide ample career development resources for the community of

kidney, urologic, and hematologic research trainees within the institution. To foster a true community, organizations will have only one U2C/TL1 program for all trainees across the entire research mission of KUH (*i.e.*, trainees may be engaged in benign kidney, urologic, or hematologic research within a single program). Furthermore, a single, consolidated application from several institutions within the same metropolitan area, which include multiple departments with a different research focus, is strongly encouraged and preferred.

Trainees under this new and revitalized program should be able to use their skills to publish in the scientific literature, compete for additional research support, and be prepared to successfully navigate the next steps toward a scientific research career. Over time, it is expected that each Institutional Network Award will actively participate in a nationwide program—formed by the collection of individual KUH U2C/TL1 awards—to train a cohort of researchers capable of achieving the scientific breakthroughs necessary to improve the care of people with kidney, urologic, and hematologic diseases.

A robust research training program incorporates research activities, professional development activities, and outreach in an interdisciplinary and collaborative environment. The new KUH "U2C/TL1" program aims to address many of these components.

Advancing Understanding of Lower Urinary Tract Symptoms and Associated Conditions

Millions of women, men, and children in the United States currently experience symptoms affecting the lower urinary tract, including pain, bladder leakage, and problems urinating. For many years, research on treating these health problems focused predominantly on organs and structures of the lower urinary tract, such as the bladder, prostate, and urethra. A not unreasonable belief was that most symptoms attributed to the lower urinary tract would eventually correlate with a particular dysfunction rooted in those tissues. Evolutions in thought over the past two decades led researchers to appreciate that not only can similar lower urinary tract symptoms result from different problems within its organs and structures, but that not all symptoms may have their origin in the urinary tract itself.

One way that lower urinary tract symptoms, or LUTS, have traditionally been captured and their severity assessed has been through the use of questionnaires—also sometimes referred to as "tools" or "instruments," depending upon the context—that allow individuals to self-report their symptoms and related issues, such as how much they are bothered by their symptoms. A question may require a person to report frequency of a symptom over a certain period of time or rate its impact on life activities. When administered in a clinical setting, questionnaires can complement physical exams to help arrive at a diagnosis and treatment plan. For example, the American Urological Association's Symptoms Score Questionnaire is used by clinicians when evaluating benign prostatic hyperplasia in men. Some questionnaires, such as the Genitourinary Pain Index, were developed and/or are used at this time mostly in clinical research settings. What many of these questionnaires have in common, however, is that when deployed in isolation, the result can be like the story of the five blind men and the elephant: each one may yield a partial description of a person's symptoms, but may not provide the complete picture needed to identify and/or better understand and manage the underlying cause(s). New research approaches incorporating multiple questionnaires to study people with LUTS, evaluation of "standard" uses of questionnaires, and the careful development of comprehensive tools for assessing LUTS have now yielded information critical both for identifying subtypes of LUTS and/or LUTS-predominant conditions, and for conducting research and clinical assessments going forward.

NEW UNDERSTANDING OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME

Chronic, often debilitating pain in the pelvic or genital areas with or without a frequent or urgent need to urinate are hallmark LUTS for a cluster of disorders referred to as urologic chronic pelvic pain syndrome (UCPPS). UCPPS serves as an umbrella term for the two most common forms of chronic pelvic pain, interstitial cystitis/bladder pain syndrome (IC/BPS, also called IC/painful bladder syndrome [PBS]), which predominantly affects women, and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which affects men. These conditions reduce quality of life and productivity and incur significant health care costs for millions of Americans.

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Despite many years of committed basic and clinical research efforts supported by the NIDDK and other research-funding agencies, the cause(s) of UCPPS has long remained elusive, as have widely or fully effective treatments. Moreover, diagnostic tests specific for UCPPS are not currently available, and many UCPPS symptoms are similar to symptoms of other conditions, such as invasive bladder cancer or endometriosis. Thus, those diseases need to be ruled out first—making IC/BPS or CP/CPPS a "diagnosis of exclusion." Historically, attempts at clinical diagnosis have included questionnaires focused on bladder and prostate symptoms and pelvic pain, along with exclusionary medical tests.

Embracing Novel Approaches: MAPP Research Network

By the mid-2000s, new perspectives from a diversity of research and clinical expertise and insights from other fields led to changes in the research approach for UCPPS. A comprehensive strategy was developed to take into account not only urologic contributors but also the influence of comorbid conditions and non-urologic factors on the onset or development of UCPPS and its symptoms—and how differences in LUTS and other symptoms among individuals diagnosed with UCPPS might be important to identifying clinically significant subgroups of patients. In 2008, the NIDDK established the multi-center Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network to conduct innovative, collaborative studies of UCPPS. Since its inception, the Network's unique approach to IC/BPS and CP/CPPS has entailed approaches that "look beyond" the bladder and prostate—the traditional focal points for study of these syndromes—to uncover meaningful new insights into the clinical and biological features of UCPPS and its relationships with other chronic pain conditions, all to set the stage for future interventions and improved clinical management.

In its first phase, the MAPP Research Network recruited 424 individuals with UCPPS—233 women with IC/BPS and 191 men with either IC/BPS or CP/CPPS—in a central, Trans-MAPP Epidemiology and Phenotyping study to better understand how these conditions progress over time and to learn if patients might fall into different, distinguishable subgroups based on differing symptoms that may arise from different causes—and, thus, may require different treatments. To achieve its many goals, the Network also recruited large numbers of "control" participants—both healthy persons without any pain syndromes, and those without UCPPS but with one or more chronic pain conditions often found in people with UCPPS, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome.

Distinguishing Characteristics: LUTS and Non-LUTS in People with UCPPS

A large part of the Trans-MAPP study consisted of participants completing a variety of questionnaires to describe not only the key symptoms of pain and bladder dysfunction, but also commonly co-occurring chronic pain conditions such as irritable bowel syndrome; stress; and issues such as depression, sleep quality, and general quality of life. While the majority have already been employed in health care settings and in clinical research to assess the impact of UCPPS on individuals and the outcomes of clinical trials, respectively, a few of these questionnaires were developed or modified specifically for use in the MAPP Research Network.

By combining outcomes of the questionnaires assessing urologic, non-urologic, and psychosocial symptoms and quality of life with "body pain mapping," MAPP researchers uncovered important new information about pain patterns and other symptoms in people with IC/BPS and CP/CPPS. Along with completing the questionnaires, the women and men participants with UCPPS were also asked to look at a "body map"—2 drawings representing the front and back of the body, partitioned into 45 numbered sites comprising 8 body regions—and to check off any site in which they had experienced pain in the past week. From the resulting data, MAPP investigators found that, whereas a quarter of participants reported pain only in the pelvic region, 75 percent reported pain in both pelvic and nonpelvic regions. Following

this observation, the investigators created three subgroups for comparison: people with pelvic pain only; people who had pelvic pain along with pain in one to two nonpelvic regions, or "intermediate pain"; and people with pelvic pain and pain in three to seven nonpelvic regions, or "widespread pain."

Intriguingly, there were no differences in pelvic pain severity or urinary symptoms across these three groups. In contrast, nonpelvic pain severity, prevalence of chronic overlapping pain conditions, worsening psychosocial health, and poor quality of life increased as the number of pain regions a person had increased. Notably, more women than men experienced widespread pain, and women were more likely to report a greater burden of nonpelvic and nonurinary symptoms and conditions as their pain locations increased. MAPP investigators also compared just the intermediate and widespread pain groups to see if there were any significant differences among study participants with UCPPS who reported nonpelvic pain. This comparison yielded similar results to those for the three-group comparison regarding pelvic pain and urinary symptoms, nonpelvic pain, and several other health measures, but also revealed more gender-specific differences. For example, compared to individuals whose pain was categorized as intermediate, men with widespread pain were more likely to have migraines and anxiety, while women were more likely to have irritable bowel syndrome and sleep disturbance.

Changing Approaches to Symptom Evaluation in People with UCPPS

The differences—and similarities—found in the Trans-MAPP body mapping study among people diagnosed with UCPPS have significant implications for better understanding the cause(s) and/or development of these syndromes and associated LUTS, for research studies on potential treatment approaches, and for clinical diagnosis and personalized care. At the same time, the Network uncovered potentially "game-changing" information about how standard questionnaire data are collected and used for people with UCPPS. In the past, many questionnaires were used to generate a composite "score" for UCPPS that combined pain (pelvic and/or genitourinary) and bladder symptoms. However, an analysis of data from a subset of questionnaires administered in the trans-MAPP study allowed Network scientists to determine that such a composite score can actually mask independent changes in each symptom area. Their analysis suggests that improvement or worsening can occur in pain independently of bladder symptoms such as urgency and frequency, and *vice versa*, and that a composite score limits the ability of researchers and clinicians to detect such changes. In addition, they found a differential impact of these key symptoms on an important comorbidity, depression: only pain symptoms were associated with depression. These MAPP Research Network findings indicate that, going forward, pain and urinary symptoms should be scored independently in UCPPS to enable more accurate research analyses and improved patient care.

TOOL DEVELOPMENT FOR UNDERSTANDING LUTS

As the MAPP Research Network was developed and conducted its studies focused on syndromes associated with a subset of LUTS, a broader challenge remained: for the wide range of LUTS, we still need to learn more about differing etiologies and potential patient subgroups to improve management and treatment of symptoms. This is true even when a person's LUTS have been linked to a problem in a structure or function in the lower urinary tract, as there still may be other factors influencing the symptoms he or she is experiencing.

Symptoms of Lower Urinary Tract Dysfunction Research Network

To address the gaps in understanding and treating LUTS, the NIDDK established the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) in 2012. LURN is an interdisciplinary, cooperative research network with several long-term goals: to identify and explain the important subtypes of LUTS in women and men; to improve the measurement of patient experiences of

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LUTS; to disseminate novel findings to researchers, clinicians, and patients; and to generate data, research tools and biological samples for future studies.

To help attain these intertwined goals, LURN enrolled nearly 2,000 women and men from among individuals presenting with LUTS to a health care provider at a LURN research site. To limit duplication with the work of the MAPP Research Network, persons with pain as a dominant LUTS were not included. Working with these participants, LURN collected clinical data, health-related quality of life assessments, and self-reported symptom measurements at "baseline," and characterized these and changes in LUTS over a 12-month period, yielding a wealth of data and enabling numerous informative studies.

Measuring Patient Experiences of LUTS

A critical goal for LURN has been to develop improved means for finding clinically important subgroups, or subtypes, among people with LUTS. Their approach was to pursue an intensive questionnaire development process, casting a wide net over LUTS in both women and men to develop the most comprehensive and nuanced instrument they could that would: (1) be able to elicit granular and precise information about symptom experience from individuals; and (2) serve as a "pool" of questions from which more targeted questionnaires could be developed and validated for clinical and research purposes. Through the development process, they also wished to explore the boundaries of what was "measurable" for LUTS—*i.e.*, to what degree unique or abnormal experiences with LUTS could be captured through a person's self-reported responses on a questionnaire.

The resulting questionnaire, called the Comprehensive Assessment of Self-reported Urinary Symptoms, or CASUS, was developed through an iterative process involving health care providers and women and men with LUTS who were not part of the LURN cohort. Vigorous steps were undertaken to ensure that the CASUS would be widely understandable, potentially translatable, and acceptable to women and men from different educational and racial/ethnic backgrounds. Emphasis was placed on including new types of questions that could get at data gaps such as specific physical sensations accompanying LUTS, particularly sensations accompanying bladder leakage (incontinence). Over 90 LUTS-related items are included in the CASUS, covering multiple symptom categories, such as frequency (day and night), sensations (including pain), urgency, urine flow, incontinence, and incomplete emptying—as well as a person's recall of any lifetime experience suggestive of LUTS. The CASUS was then put through its paces with over 1,000 participants from the LURN Observational Cohort Study. Their responses not only demonstrated that CASUS could be used in symptomatic persons to obtain a wide range of information about LUTS, but also revealed intriguing sex/gender differences in sensations associated with urinary incontinence that can be explored to look for potential causes.

Adapting CASUS for Practical Application

The CASUS is an extensive menu of items that can be used in concert with other data from the LURN Observational Cohort Study to delve deeply and pursue extensive subgrouping of LUTS. However, it might not be easily administered in all situations, either research or clinical. At the same time, LURN investigators wanted to ensure that the aspects of CASUS that were missing from other assessment tools for LUTS were still retained as much as possible.

Starting from the CASUS, LURN investigators proceeded to develop, through a multi-step process, two scaled-down questionnaires—one for research use, and one for clinical use. These became the LURN Symptom Index-29 (LURN SI-29) and the LURN SI-10. The LURN SI-29 is intended to be a representative outcome assessment for use in research; it includes 29 items covering urgency, incontinence, voiding difficulty, nighttime voiding (nocturia), and pain. The briefer LURN SI-10 for clinical use is intended to elicit responses that would indicate whether there is a need for further clinical investigation and/or intervention; it includes 10 items assessing frequency, nocturia,

urgency, incontinence, bladder pain, and post-voiding symptoms, and an additional item on symptom bother. Both have been validated against other questionnaires representing different aspects of LUTS. Both are also meant to be used with either women or men, rather than needing separate instruments.

Another aspect important to the application of CASUS, its derivatives, and other LUTS questionnaires is the accuracy of recall in self-report—*i.e.*, most questionnaires ask individuals to provide assessments of their symptoms within a specified time, such as the past 7 days. Because this could affect the robustness of LUTS data obtained via CASUS, *etc.*, LURN investigators performed another study, in which they obtained daily responses to 18 CASUS items over 7- and 30-day periods, averaged them, and compared them to the corresponding 7- or 30-day recall versions of responses to the items. This study demonstrated good tracking of recall responses with averaged daily responses, with minimal bias—*i.e.*, over- or underreporting of symptoms—supporting the continued use of both 7- and 30-day recall questionnaires in the assessment of LUTS.

LOOKING TO THE FUTURE

Much remains to be learned about LUTS—their causes, development, and how best to manage and treat people experiencing these symptoms. Through multiple activities—including the use and development of improved questionnaires—in MAPP, LURN, and other investigations such as the NIDDK's Prevention of Lower Urinary Tract Research Consortium (PLUS), more comprehensive subgrouping of people with LUTS and LUTS-predominant conditions is now possible, with important implications for future trial design and clinical management.

PERSONAL PERSPECTIVE

Paving a Path to Personalized Kidney Care Through Participation in Research

Acute kidney injury (AKI) and chronic kidney disease (CKD) impose a significant personal and global health burden; however, only a few therapies are available for CKD, and none currently exist for AKI. Development of drug therapies for AKI and CKD has been hampered by many practical research issues, such as imperfect animal models, the inability to identify and prioritize molecular therapeutic targets in human kidneys, and a poor understanding of the underlying biology of human AKI and CKD. A growing consensus based on research findings suggests that neither CKD nor AKI are singular diseases; rather, there are specific subgroups of these diseases that are driven by different biological pathways. Thus, a better understanding of the biological pathways that lead to the diversity of kidney diseases will likely inspire the development of more effective individualized treatment options, an approach referred to as "precision medicine." In 2017, the NIDDK launched the Kidney Precision Medicine Project (KPMP)—a bold research program that is beginning to chart a course toward a more personalized approach to clinical care for people with kidney diseases.

THE KIDNEY PRECISION MEDICINE PROJECT

Imagine a future where a person with kidney disease could work with clinicians to answer important, patient-centered questions, such as: "What type of kidney disease do I have?" "What will happen to me?" "What can I do about it?" In this vision, a nephrologist (kidney disease specialist) might: (1) evaluate the person's disease profile using blood and urine tests, (2) visualize the kidney in real-time using advanced imaging technologies, (3) identify and biopsy areas of kidney damage, (4) analyze the biopsy tissue using a kidney tissue atlas—a tool designed to classify the location and health of kidney tissue components, and thereby (5) select the appropriate therapy to start individualized treatment.

The KPMP strives to achieve this individualized approach to patient care by working toward several goals with the overall objective of bringing precision medicine to AKI and CKD: to ethically and safely obtain and evaluate human kidney biopsies from research participants with a wide range of AKI or CKD—a procedure not typically done in the United States; create a kidney tissue atlas; define disease subgroups; and identify critical cells, extracellular components, and pathways that can be targeted for developing novel therapies. Researchers are now poised to begin constructing a kidney atlas due to the maturation of sophisticated technologies over the past several years, but only with the invaluable contributions of study participants. (See inset for the story of a KPMP participant.)

HUMAN KIDNEY BIOPSIES—THE KEY TO UNLOCKING THE FUTURE OF PERSONALIZED KIDNEY CARE

In order to catalyze research toward personalized kidney care, KPMP research requires an essential component—human kidney biopsies. For nephrologists to take tailored approaches to kidney care, specific subtypes of AKI or CKD will need to be identified. However, advancing science to a point where disease subtypes are well defined will

require technological leaps that can only be made by analyzing biopsy tissue from many people with kidney disease—altruistic study participants who will undergo the biopsy procedure, which carries some personal risk, to support the goals of KPMP to help people with kidney diseases in the future.

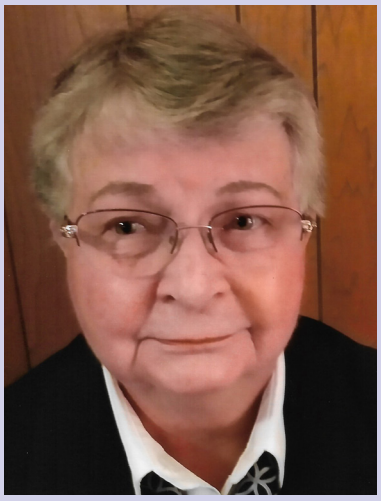
Human kidney biopsies obtained through the KPMP are being analyzed to identify new molecular "markers" that will reveal differences among cells and tissues in exquisite detail to define specific kidney structures. Markers characterized by the KPMP will help establish a complex kidney atlas that can classify and locate different cell types, cell states (such as healthy, injured, dying, recovering, undergoing repair), and molecules involved in the progression of kidney disease. These new markers will then be linked to important clinical outcomes. The emerging kidney tissue atlas will be used as a foundation to better understand the cellular and molecular diversity of kidney diseases, and help define specific disease subgroups. This knowledge can inform decision making by pathologists, nephrologists, and people with AKI and CKD.

STUDY PARTICIPANTS PAVE THE PATH FORWARD

KPMP's bold, innovative approach hopes to build a foundation for new therapeutic development. However, this research would not be possible without the generosity and courage of study participants providing research kidney biopsies—contributions that are deeply appreciated by the research and clinical communities. For the patients KPMP aims to serve, currently kidney biopsies are of unknown individual benefit, and the biopsy procedure carries some risk for well-defined complications, such as bleeding, pain, and very rarely death. Thus, a central component of the KPMP has been to design the study with great care to build a strong case to explain to people with kidney diseases and their health care providers how biopsies could have long-term benefit because of their critical role in advancing research progress toward precision medicine. Toward this effort, patients have been an important part of the research design process, helping to tackle issues such as community engagement, ethics, biopsy safety, and data-sharing strategies.

Over time, results and resources from the KPMP are expected to dramatically improve scientists' understanding of human kidney diseases, which in turn is likely to catalyze the development of new therapies. Biopsy results will likely become more informative to clinical care as pathologists and nephrologists can better predict a drug's effectiveness based on an individual's specific kidney profile. Through their participation in KPMP, individuals with kidney diseases are helping to understand their own conditions, and paving a path toward a brighter future for people with kidney diseases.

HARRIET'S STORY



Harriet, pictured here, participated in an NIDDK-supported research study charting a course toward personalized treatments for kidney diseases

For years, 77-year-old Harriet underwent regular medical tests to help understand an unusual pattern of test results that perplexed her physicians. "They were doing blood samples every 6 months … that started about 10 years ago" she recalls. "I started to get

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strange numbers that were unexplained.... They tried various medications and nothing seemed to be explaining what was happening." The doctors had found excess protein in the urine, a condition known as "proteinuria" that is an indicator of kidney dysfunction. Surprisingly, however, there were no other clinical markers of kidney disease, making it difficult to diagnose precisely her condition. Her physicians had also prescribed medications to control blood pressure and manage her prediabetes—factors that could affect kidney health.

About 2 years ago, one of her physicians referred her to a nephrologist for kidney-specific medical care at the Cleveland Clinic, which is not too far from her home. The nephrologist monitored her health for about a year, observing similar test patterns. The specialist then recommended that she consider participating in a new research study—the Kidney Precision Medicine Project (KPMP)—that was taking place at several sites across the United States, including the Cleveland Clinic, and enrolling participants to undergo kidney biopsies. Participation in KPMP could not only shed some light on her own condition, but also contribute to a potentially important research effort. Harriet, a former paint and coatings development researcher trained in chemistry, says that she, "having a research and development background, was kind of excited about it."

Within weeks of enrolling in KPMP and meeting with the research team, Harriet underwent a biopsy procedure in January 2020 to collect samples from her left kidney. "The intention was to take between three and five samples, so that the samples could be sent to several different research centers, and one could be kept here at Cleveland Clinic," she explains. The procedure started off well, "up until they attempted to take the third sample and had some trouble with that. So they went in and took the fourth sample, and then were very satisfied with the three good samples that they had." With three good samples in hand, the research team finished the procedure and Harriet headed home. The research team had explained to Harriet that there could be complications from the biopsy, but thankfully there were none. As she recalls, "they said I could expect ... some kind of bleeding. I didn't have any kind of interior or exterior bleeding. It went very, very well."

Shortly after the biopsy collection, one of the KPMP physician-scientists called Harriet not only to confirm that the quality of the samples was good, but also to share some interesting news: analysis of the biopsy revealed that she has a relatively rare kidney condition called fibrillary glomerulonephritis, in which the body produces unusual proteins that become trapped in and disrupt the filtration units of the kidney. This new diagnosis helped explain the unusual pattern of blood and urine tests, illustrating the utility of biopsy collection in classifying kidney diseases. As Harriet recounts, it was "an unusual thing that they weren't expecting to find." She added that the doctors were excited that they had finally found a diagnosis to explain the test results over the years. Now with this new information, she is better positioned to strategize future treatment plans with her medical providers.

"They tried various medications and nothing seemed to be explaining what was happening," says Harriet of her test results showing an unexplained excess of protein in her urine, prior to her diagnosis through participating in a clinical research study.

Post-biopsy recommendations by the KPMP staff have been relatively straightforward. She has had one in-person visit with Cleveland Clinic staff and several conversations by phone. Research is ongoing to develop drugs for her particular kidney condition, but there are currently no effective therapies in common use. However, Harriet has

been encouraged to continue with fairly standard practices, such as maintaining a healthy diet by limiting sodium and sugar intake. Harriet has been doing well in the months following the biopsy procedure. "I have no unusual side effects, nothing seems to be out of the ordinary," she says. However, KPMP staff are closely monitoring her blood tests, and her kidney condition continues to be a problem. "They're keeping a good eye on what's going on, but the protein spillage [into the urine] has continued and increased."

"The exciting part was that the research is being done on the molecular level. So maybe they will be able to look into the mechanism that is behind what my problem is," says Harriet of her participation in the NIDDK's Kidney Precision Medicine Project, which facilitated her diagnosis of a rare kidney disease.

The COVID-19 pandemic has affected Harriet's daily life, as it has for everyone. She continues to be an avid reader, care for her husband, and walk her dog. But she misses being an usher with the Cleveland Orchestra—a role that she has enjoyed for 11 years. Because of the pandemic, the orchestra cancelled their performances. "I knew nothing about classical music before I started ushering, and I have learned a tremendous amount and a great appreciation has grown for it," she says.

Harriet's career in research and development has shaped her perspective on the importance of KPMP in therapeutic development. "I understand the importance of having good samples to work with, and unusual samples to work with," she explains. "The exciting part was that the research is being done on the molecular level. So maybe they will be able to look into the mechanism that is behind what my problem is." She adds that "since they can look at an actual piece of tissue … they can possibly determine what a better course of treatment would be."

Harriet is hopeful that her participation will help others who have kidney disease. Of KPMP, she notes the "importance of having this kind of research program" because "more understanding of what maybe caused [her condition] or what they can do to control it, would be … beneficial." Indeed, thanks to the dedication of Harriet and other participants, KPMP research holds tremendous promise to improve the health and quality of life of people with kidney diseases.