

# NIDDK

Recent Advances & Emerging Opportunities

## Kidney, Urologic, and Hematologic Diseases

January 2022

This is a chapter from the NIDDK's Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK's mission and is available at:

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U.S. Department of Health and Human Services  
National Institutes of Health  
National Institute of Diabetes & Digestive & Kidney Diseases



National Institute of  
Diabetes and Digestive  
and Kidney Diseases

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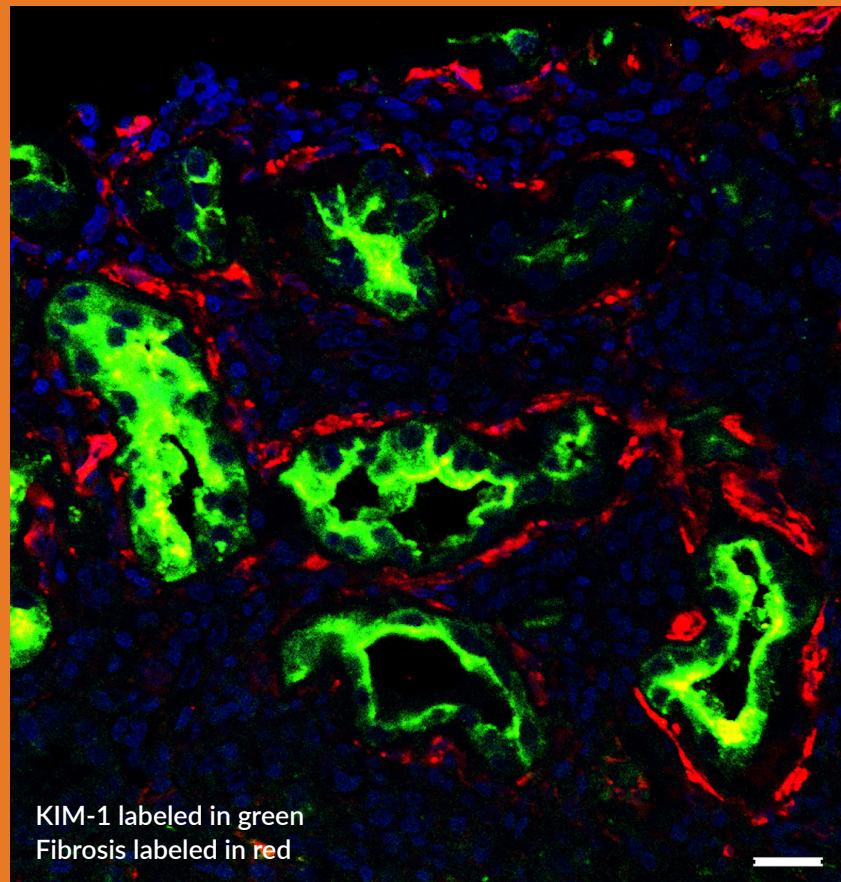
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As described later in this chapter, the protein Kidney Injury Molecule-1 (KIM-1) is highly expressed in kidney proximal tubules of individuals with diabetic kidney disease (DKD), but not of people without DKD. Further analyses revealed that in kidneys from individuals with DKD, KIM-1-positive tubules were surrounded by fibrosis, which is the deposition of large amounts of collagen-rich connective tissue that can lead to organ damage. Inhibition of KIM-1 led to reduced fibrosis, suggesting that KIM-1 represents a novel target for developing treatments for DKD.

*Image provided by Drs. Joseph Bonventre, Amrendra Ajay, and Yutaro Mori, Brigham and Women's Hospital, Harvard Medical School. Reprinted from Cell Metabolism, 33/5, Mori Y, Ajay AK, Chang J-H, Mou S, Zhao H, Kishi S, Li J, Brooks CR, Xiao S, Woo H-M, Sabbiseti VS, Palmer SC, Galichon P, Li L, Henderson JM, Kuchroo VK, Hawkins J, Ichimura T, and Bonventre JV, KIM-1 mediates fatty acid uptake by renal tubular cells to promote progressive diabetic kidney disease. 1042-1061, 2021, 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.

An estimated 37 million American adults have impaired kidney function—also called chronic kidney disease (CKD).<sup>1</sup> 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. CKD can also result from other factors, as noted below.

*An estimated 37 million American adults have chronic kidney disease.<sup>1</sup>*

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.<sup>2</sup> 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 Asian Americans.<sup>2</sup> Compared to the non-Hispanic population, Hispanic Americans had 1.5 times the risk for kidney failure.<sup>2</sup>

*In 2018, over 783,000 patients received treatment for end-stage renal (kidney) disease.<sup>2</sup>*

The NIDDK supports a significant body of research aimed at understanding the biology underlying CKD and developing treatment strategies. The chronic renal diseases program supports basic, translational, 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 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

<sup>1</sup> Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2021*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2021.

<sup>2</sup> 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.



uremic syndrome. 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.

*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 chronic kidney disease and end-stage renal disease.<sup>2</sup>*

Urologic diseases and conditions 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 urinary tract infections and urinary stone disease, two of the most common and costly urologic conditions affecting people in the United States. Urinary incontinence is another prevalent problem. Based on national public health surveys conducted over several years, it is estimated that about 54 percent of women 20 years and older experience urinary incontinence each year. Urinary incontinence was self-reported by approximately 15 percent of men surveyed.<sup>3</sup> Many suffer in silence due to embarrassment and lack of knowledge about treatment options available.

*About 54 percent of women 20 years and older experience urinary incontinence each year.<sup>3</sup>*

Many people are also living with one of a cluster of disorders collectively called urologic chronic pelvic pain syndrome (UCPPS). The two most common examples of UCPPS are interstitial cystitis/bladder pain syndrome (IC/BPS)—also known as IC/painful bladder syndrome (PBS)—and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). 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.<sup>4</sup> 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 IC/BPS.<sup>5</sup> 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.

*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 interstitial cystitis/bladder pain syndrome.<sup>3</sup>*

Research on UCPPS is one example of how the NIDDK is seeking a broad-based understanding of symptoms affecting the lower urinary tract (LUTS). LUTS—including pain, bladder leakage, and problems urinating—are not always associated with discrete conditions or tissue dysfunctions, different conditions can share the same symptoms, and symptom causes may actually lie outside the urinary tract. For example, urinary incontinence symptoms have been linked to anxiety disorders in some cases. For the wide range of LUTS, we still need to learn more about causes and contributing factors 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. Moreover, researchers now have a better appreciation that clinical end points for treatments do not always match up with individual preferences for a satisfactory outcome. Thus, the NIDDK is supporting multiple efforts to identify and understand different subgroups of people with LUTS through improved measurement of their symptom experiences that can inform future therapeutic strategies. Simultaneously, the NIDDK is supporting research to better understand factors that contribute to bladder health over the lifespan, with the ultimate goal of preventing LUTS to begin with.

<sup>3</sup> *Urological Diseases in America, 2018 Addendum. NIDDK, NIH Publication Number 12-7865, 2018.*

<sup>4</sup> *Berry SH, et al. J Urol 186: 540-544, 2011.*

<sup>5</sup> *Link CL, et al. J Urol 180: 599-606, 2008.*

*Blood diseases and disorders—some of which cause severe, debilitating pain, and premature death—affect millions of Americans.*

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 (hematopoietic) system in order to develop effective treatment strategies. Blood diseases and disorders—some of which cause severe, debilitating pain, and premature death—affect millions of Americans. These inherited and acquired diseases can affect red and white blood cells, platelets, bone marrow, or blood vessels. Research efforts include studies of a number of nonmalignant blood diseases, including sickle cell disease, the thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, thrombocytopenia, the anemia of inflammation and of chronic diseases, hemochromatosis, HIV-associated blood-related dysfunction, and bone marrow failure. The NIDDK also supports research on the basic biology of adult blood (hematopoietic) stem cells, which are used clinically in bone marrow transplants and may have broader application in gene therapy research.

Highlights of recent advances from NIDDK-supported research on kidney, urology, and hematology topics are provided in this chapter.

## CLINICAL RESEARCH ON KIDNEY DISEASE

### **Robust Research Pipeline Ensures Exquisite Data Quality Control, Paving the Path Toward Personalized Kidney Care:**

A large team of scientists has developed and tested a robust research pipeline for rigorously collecting and analyzing kidney biopsy samples; these analyses will be essential for catalyzing research toward personalized care for people with kidney diseases. Few therapies are currently available for treating chronic kidney disease and acute kidney injury—two relatively common types of kidney diseases. The NIDDK's Kidney Precision Medicine Project (KPMP) aims to identify previously elusive cells, molecules, and pathways involved in kidney disease progression by harnessing sophisticated research technologies. Ultimately, KPMP's goals are to construct a high-resolution three-dimensional kidney “atlas,” define kidney disease subgroups, and identify new therapeutic targets, which together will provide a foundation for personalized approaches to kidney care.

A central component of KPMP is the procurement of kidney biopsies from people with and without kidney diseases across multiple U.S. locations. These biopsy samples are then divided and shipped to different laboratories for analysis to identify a range of molecules (e.g., genetic material, proteins, and metabolites) and cells in the kidney that are associated with health or disease states. Importantly, reproducibility of research results across KPMP sites requires standardized processes and high levels of quality control at each step, such as biopsy procurement, preservation, storage, and analysis, as well as data generation and validation. In a recent report, KPMP scientists detailed this enormous collaborative undertaking, in which they carefully developed a series of protocols to generate an integrated “follow the tissue” pipeline that will maximize the information gleaned from the precious biopsy samples. The researchers then tested the pipeline in a pilot experiment using adult human kidney tissue from a single source. The pilot experiment demonstrated that the pipeline was indeed robust and results were reproducible at five laboratories. The experiment also revealed some areas for improvement, such as inconsistencies in temperature states during shipping and the need for some additional surrounding tissue to optimize a particular imaging technique. These issues will be addressed and corrected as the KPMP study moves forward.

The establishment of this robust “follow the tissue” pipeline was essential for KPMP to begin generating rigorous and reproducible data that will accelerate research toward personalized kidney care. This framework could serve as a model for developing organ atlases with limited tissue to advance precision medicine research for other diseases.

*El-Achkar TM, Eadon MT, Menon R, ... Jain S; for The Kidney Precision Medicine Project. A multimodal and integrated approach to interrogate human kidney biopsies with rigor and reproducibility: guidelines from the Kidney Precision Medicine Project. *Physiol Genomics* 53: 1-11, 2020.*

*Kidney Precision Medicine Project (KPMP) scientists have developed a robust research pipeline for rigorous and reproducible analysis of human kidney biopsies—an essential foundation for paving the path toward personalized care for people with kidney diseases.*

### **Multidisciplinary Approach Uncovers Potential New Biomarker for Kidney Function:**

A new study has revealed a potential novel blood-based biomarker for assessing kidney health. Normally, the kidneys filter out a wide variety of molecules from the blood, preventing buildup of wastes and toxins. Currently available blood tests to assess kidney function rely on detecting higher levels of such molecules in the blood; however, it would be useful to have biomarkers of kidney health and function that are independent of the kidney's filtration process. Researchers initially identified a candidate biomarker, a protein called testican-2, when looking for proteins that are secreted by the kidneys into the blood rather than cleared from it. Using an advanced technique called aptamer-based profiling, they quickly assessed over 1,300 proteins present in blood samples available from 22 patients with cardiovascular disease and found six proteins present at higher levels in blood exiting the kidney than that entering it, with testican-2 showing the highest relative increase. To determine whether this discovery might have clinical significance, the team applied the same advanced technique to samples available from over 3,500 participants in two large clinical study populations—one African American, the other White—this time to assess associations between blood proteins and standard measures of kidney function. Among their findings was the observation that testican-2 levels correlated directly with standard measures of kidney function in both cohorts. Moreover, when they analyzed follow-up health information available from a subset of these participants, they found that having relatively higher levels of testican-2 at study entry was associated with a lower rate of decline in kidney function in both cohorts and a decreased risk of new-onset chronic kidney disease.

Given the potential of testican-2 as a biomarker for kidney health, the team also performed a series of molecular experiments to better characterize testican-2 and gain insight into its possible function in human kidneys. These experiments revealed that human testican-2 is encoded by the gene *SPOCK2* and is expressed exclusively by podocytes—highly specialized cells in the kidney that prevent loss of critical blood proteins into the urine during the filtration process. Additional experiments with laboratory-grown cells suggested that testican-2 may enhance formation of the tiny blood vessels involved in kidney filtration, but its actual function remains unknown.

Together with data captured about other kidney proteins during the course of the study, these findings lay the

foundation for future studies, such as targeted blood tests for testican-2 and direct studies of its association with kidney disease outcomes. Additional research could lead to new clinical tools for assessing kidney health and decline that could be a significant improvement over current methods.

*Ngo D, Wen D, Gao Y,...Rhee EP. Circulating testican-2 is a podocyte-derived marker of kidney health. PNAS 117: 25026-25035, 2020.*

### **IDENTIFYING THERAPEUTIC TARGETS FOR KIDNEY DISEASES**

#### **Zeroing in on the Role of KIM-1 in Diabetic Kidney**

**Disease:** Researchers have found that the protein KIM-1 plays a critical role in progression of diabetic kidney disease (DKD) and thus may serve as a promising therapeutic target. Diabetes is the most frequent cause of chronic kidney disease. DKD generally has been thought to result from damage to the glomerulus, which is a specific segment in each of the kidney's roughly one million nephrons (functional filtration units). However, abnormalities in a different segment of the nephron called the proximal tubule (PT) may appear earlier than glomerular injury during DKD progression. Previously, researchers discovered that a protein called kidney injury molecule-1 (KIM-1) was associated with PT damage at early stages of DKD, and found that elevated levels of circulating KIM-1 predicted disease progression in people with type 1 diabetes. These and other findings suggested a PT-specific role for KIM-1 in DKD progression.

The scientists have now extended their previous research, reporting that KIM-1 protein levels in kidney PT cells were higher in biopsy samples from people with DKD (1 female, 6 males) than from people with other forms of kidney disease that do not exhibit tubule damage (3 females, 2 males). The scientists conducted a series of experiments with cultured cells, as well as with mouse models of diabetes, and showed that KIM-1 is required for PT cells to take up (i.e., to bring materials from the outside to the inside of the cell) a protein called albumin only when it is bound by a specific fatty acid known as palmitic acid (PA). The scientists showed that PA-albumin uptake leads to PT cell injury, as well as other types of kidney damage. Furthermore, genetic deletion of a portion of KIM-1, resulting in a nonfunctional protein, prevented DKD in an experimental model of male mice, suggesting that KIM-1 is required for kidney injury and resulting disease. The

scientists then tested more than 14,000 small molecules for their ability to prevent KIM-1-mediated PA-albumin uptake in cultured cells, and identified TW-37 as a candidate molecule. Mice treated with TW-37 were protected from PA-induced kidney damage, as were human kidney cell aggregates tested in culture. Together, these findings strongly implicate KIM-1 as a potential therapeutic target in people with DKD, and TW-37 could be a promising candidate as a small-molecule drug. Additional studies are needed to explore these possibilities.

Mori Y, Ajay AK, Chang J-H,...Bonventre JV. KIM-1 mediates fatty acid uptake by renal tubular cells to promote progressive diabetic kidney disease. *Cell Metab* 33: 1042-1061, 2021.

**Exploring the Role of Exosomes in the Progression of Polycystic Kidney Disease:** A recent report described a previously unknown role of exosomes in the progression of polycystic kidney disease and identified a compound capable of delaying cyst growth in mouse models of the disease. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of chronic kidney failure; most people with the disease have mutations in the *PKD1* gene. ADPKD is characterized by the growth of numerous fluid-filled cysts in the kidneys. Over time, growth of these cysts results in enlarged kidneys in which normal tissue is displaced and kidney function is impaired, sometimes quite severely. The fundamental processes that control ADPKD progression remain elusive. The exosome is a tiny sac-like structure that is formed inside a cell and contains some of the cell's proteins, DNA, and RNA. Many types of cells contain exosomes which are released into the blood or urine. Exosomes, therefore, can serve as cellular messengers as they transfer proteins, DNA, and RNA into other cells. Exosomes have received much attention lately for their involvement in human diseases such as cancer, but the role exosomes may play in some other diseases, such as ADPKD, is currently unknown.

Researchers have now shown that exosomes obtained from the urine of people with ADPKD stimulated a significant increase in the number of mouse kidney cells (*i.e.*, increased proliferation) in cell culture compared to exosomes obtained from healthy people. These results suggested that ADPKD urinary exosomes contain a critical factor(s) capable of activating PKD-associated signaling pathways to ultimately increase kidney cell proliferation, which in turn could contribute to the growth of cysts. Intriguingly, mouse kidney cells treated with urinary exosomes from healthy people formed

kidney-like tubule structures in three-dimensional gels while mouse kidney cells treated with urinary exosomes from people with ADPKD formed cyst-like structures in gels. Treatment with exosomes obtained from mouse cells containing *Pkd1* gene mutations promoted cyst growth in a mouse model of ADPKD compared to the same mouse model not treated with exosomes. Furthermore, the exosome inhibitor GW4869, which blocks exosome release into the blood, delayed cyst growth in a mouse model of ADPKD. The results of this study suggest that targeting exosome secretion may be a potential therapeutic strategy to reduce or delay cyst formation in people with ADPKD.

Ding H, Li LX, Harris PC, Yang J, and Li X. Extracellular vesicles and exosomes generated from cystic renal epithelial cells promote cyst growth in autosomal dominant polycystic kidney disease. *Nat Commun* 12: 4548, 2021.

*For the first time, small packages of cellular components, called exosomes, have been shown to play a role in mice and in kidney cells grown in the laboratory and targeting their secretion may have therapeutic benefit for people with autosomal dominant polycystic kidney disease.*

## RESEARCH ON LOWER URINARY TRACT SYMPTOMS AND DISORDERS

**A New Approach to Studying the Links Between Bladder and Brain Activity in People:** Researchers have demonstrated the efficacy of a new, more natural approach to studying bladder function in people. Many studies of people with urologic problems, such as bladder pain or sudden urinary urgency, have involved artificially filling the bladder with liquid using a catheter and simultaneously visualizing brain activity using magnetic resonance imaging (MRI). Such studies have helped identify brain regions and networks involved in perceiving and responding to changes in bladder fullness, in the hope of finding ways to alleviate suffering in people with urologic symptoms that are as yet hard to explain or treat. However, this research approach, while having advantages such as control over the amount of liquid inserted, comes with potential drawbacks—for example, the procedure of catheterization itself can cause discomfort and anxiety in study participants, thereby influencing what is seen in brain scans.

To see whether a more natural bladder-filling strategy would be viable and possibly superior as a study method,



researchers in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network studied the brain's response to natural bladder filling in study participants without urologic problems. Sixty-two healthy men and women were asked to drink about 12 ounces of water after first voiding their bladders; 40 minutes later, they underwent an MRI brain scan for 10 minutes, emptied their bladders into a urine collection container, and underwent a second 10-minute scan. Participants were also asked to report the degree of urgency they felt at different times during the procedure—just after drinking the water, 20 minutes later, and both before and after each MRI scan. The majority of participants responded to the test procedure with an increasing feeling of urinary urgency that peaked by the end of the first scan and was relieved when they voided. More intense feelings of urgency correlated with larger void volumes—a proxy measure of bladder fullness. The researchers found that activity in specific brain regions and networks associated with bladder filling and voiding—from sensory recognition to physical response—not only was detectable, but also correlated with perceived urinary urgency and with void volumes.

This study provides proof that a more natural bladder filling method that avoids invasive catheterization is effective for studying brain activities important to urologic function and correlating them with people's symptom experiences. Such an approach should be easier to implement and help researchers perform studies in larger and more diverse groups of people. Already, it is being used to study symptomatic participants in the MAPP Research Network, and should advance overall efforts to study people with underlying urologic diseases, disorders, and symptoms.

Mawla I, Schrepf A, Ichescio E,...Kutch JJ. Natural bladder filling alters resting brain function at multiple spatial scales: a proof-of-concept MAPP Network Neuroimaging Study. *Sci Rep* 10: 19901, 2020.

***A recent report suggests that researchers will be able to make new, clinically relevant discoveries about the role of the central nervous system in urologic problems using an approach that is much less invasive than has been used previously.***

### Potential Therapeutic Target for Erectile Dysfunction

**Following Prostate Cancer Surgery:** Researchers have identified a nerve regeneration pathway that could be targeted to reverse erectile dysfunction (ED) caused by surgery. ED is a condition in which one is unable to get or maintain a penile erection firm enough for satisfactory sexual activity. Notably, many men experience ED after prostate cancer surgery. ED may occur if nerves that regulate blood flow to the penis, called cavernous nerves, are inadvertently damaged or removed during surgery. Unfortunately, existing treatments are rarely effective for men with ED following prostate cancer surgery.

Investigators recently described a series of experiments in male rodents that highlight the important role of a protein called fidgetin-like 2 (FL2) in the regeneration of neurons, or nerve cells. One way to assess neuronal regeneration is to measure growth of the axon, a specialized cellular extension neurons use to transmit signals throughout the body. The researchers found that mouse neurons genetically engineered to no longer produce FL2 protein had significantly longer axon growth compared to neurons with normal levels of FL2. This finding suggested that FL2 acts as a negative regulator of axon growth and that its absence might facilitate neuron growth. To test this, the researchers used a technique employing small interfering RNAs (siRNAs)—short strips of genetic material—to effectively “turn off” the *FL2* gene in a rat model of cavernous nerve injury that mimics what can occur in human prostate cancer surgery. In this experiment, *FL2*-siRNAs, packaged in nanoparticles, were topically applied to crushed cavernous nerves immediately after injury. After 4 weeks, the erectile response of the rats treated with *FL2*-siRNAs was significantly improved compared to that of animals treated with controls (no *FL2*-siRNAs). In addition, applying *FL2*-siRNA treatment to rats with severed cavernous nerves resulted in seven of eight animals exhibiting visible nerve regeneration and erectile response 2 weeks later, whereas rats treated with scrambled siRNA had no visible nerve regrowth.

These findings demonstrate that depleting FL2 protein in neurons enhances their regeneration potential and suggest that approaches targeting production of this protein may lead to promising therapeutic strategies for ED caused by prostate cancer surgery.

Baker L, Tar M, Kramer AH,...Sharp DJ. Fidgetin-like 2 negatively regulates axonal growth and can be targeted to promote functional nerve regeneration. *JCI Insight* 6: e138484, 2021.

## BLOOD STEM CELLS AND THE BONE MARROW

### Elucidating New Mechanism for Blood Stem Cell Migration from the Bone Marrow:

Scientists recently reported that a type of nerve cell plays an important role in the migration of blood stem cells from the bone marrow and into the circulation—potentially facilitating their collection for therapeutic uses. Blood stem cells—also called hematopoietic stem cells, or HSCs—have the potential either to self-renew into two identical daughter stem cells or to give rise (mature) into specialized cell types: red blood cells, white blood cells, or platelets. HSCs reside in specialized microenvironments in the bone marrow from which they can be mobilized via physiological stressors, such as significant blood loss, to enter the blood circulation and mature into all the body's blood cells. However, the mechanisms by which HSCs migrate out of the bone marrow are largely unknown.

In new research using both female and male mice, scientists showed that the specialized microenvironments in the bone marrow also contain a high density of sensory nerves called nociceptive nerves. Found throughout the body, these nerves are normally important to pain perception and prevention of tissue damage, sending signals to the spinal cord and brain in response to a noxious (painful) stimulus. So what are nociceptive nerves doing in the bone marrow? It turns out that a molecule released by these specialized nerve cells, called CGRP, acts in concert with other signals in the bone marrow to drive a cascade of events ultimately instructing the HSCs to migrate and enter the blood circulation. In the mid-1990s, a report described how capsaicin, an ingredient in chili peppers, interacts with its cell surface receptor to “turn on” nociceptive nerves in the gastrointestinal tract to produce a burning sensation. With this knowledge in mind, the scientists asked whether capsaicin could affect HSC migration out of the bone marrow. Intriguingly, mice that consumed a capsaicin-containing spicy food diet were found to have significantly enhanced HSC migration into the bloodstream compared to mice fed a standard diet. Targeting the nociceptive nervous system could, therefore, represent a strategy to improve the yield of HSCs needed for stem cell-based therapeutic protocols.

Gao X, Zhang D, Xu C, Li H, Caron KM, and Frenette PS. Nociceptive nerves regulate haematopoietic stem cell mobilization. *Nature* 589: 591-596, 2021.

### New Insight into the Mouse Blood Stem Cell Aging

**Process:** New research has identified changes in the microenvironment of the bone marrow that contributes to the aging process of blood (hematopoietic) stem cells (HSCs). The HSC is a type of adult stem cell found in the bone marrow that can self-renew and develop into any type of white blood cell (e.g., B-cell, T-cell, and natural killer cell), oxygen-carrying red blood cells, and a variety of immune cells (e.g., megakaryocytes, monocytes). Because they can effectively regenerate any type of blood cell the body needs, HSCs are recognized as a new way to treat various diseases such as cancers, autoimmune diseases, and nonmalignant blood diseases such as sickle cell disease. However, previous research has shown that for unknown reasons, as people age, the capacity of their HSCs to develop into different types of blood cells diminishes.

*New research shows that pain sensory nerves play a role in the migration of blood stem cells from the bone marrow into the blood circulation, providing insights that could help to improve stem cell-based therapeutic protocols.*

In this study, investigators sought out changes in the aging bone marrow of mice that may contribute to the diminished capacity of HSCs to develop into different types of blood cells. They reported that characteristic hallmarks of aging HSCs in middle-aged female mice are linked to a reduction in the level of a hormone called insulin-like growth factor 1 (IGF1) in the bone marrow. Interestingly, IGF1 treatment of HSCs from middle-aged female mice restored characteristics of younger, healthier HSCs. These findings suggest that therapeutic strategies aimed at increasing IGF1 levels in the bone marrow may be able to halt or partially reverse HSC aging, and, thereby, boost HSC function through middle age and perhaps longer.

Young K, Eudy E, Bell R,...Trowbridge JJ. Decline in IGF1 in the bone marrow microenvironment initiates hematopoietic stem cell aging. *Cell Stem Cell* 28: 1473-1482.e7, 2021.

# Developing Vascular Access Technologies To Improve Kidney Disease Treatment—Highlights of Small Business Innovation Research

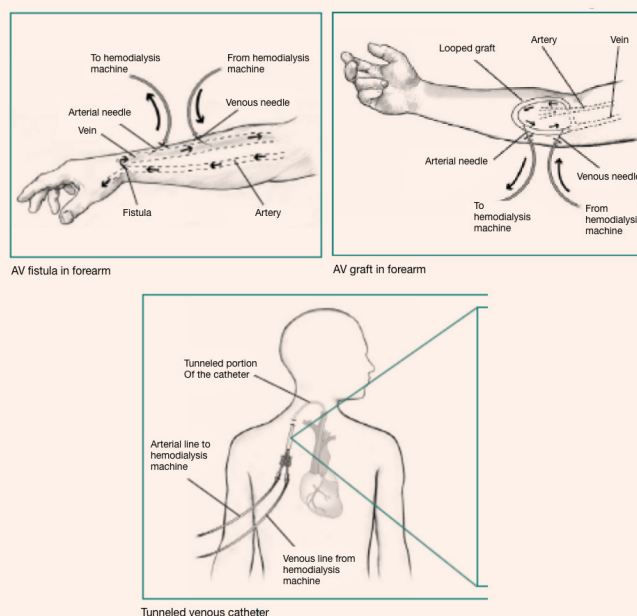
The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs together are one of the largest sources of early-stage capital for technology commercialization in the United States. The SBIR program allows U.S.-owned and -operated small businesses to engage in federal research and development (R&D) that has a strong potential for commercialization. The NIDDK's program supports health and life science companies that are creating innovative technologies that align with the Institute's mission to improve health and save lives. A key objective of the program is to translate promising technologies to the private sector and enable life-saving innovations to reach consumer markets.

As mandated by U.S. law, SBIR and STTR applications—like other grant applications—undergo a two-step peer-review process. SBIR and STTR applications that are approved are then funded through a congressionally mandated set-aside share of the Institute's budget in the form of grants. (Additional information is available at <https://sbir.nih.gov>.)

## FEATURE HIGHLIGHT: SBIR PROJECTS ON VASCULAR ACCESS FOR KIDNEY DIALYSIS

The NIDDK supports SBIR grants in many areas across its mission. This feature highlights just one of those research areas as an example—developing technologies to improve vascular access for kidney dialysis treatment. People whose kidneys no longer function sufficiently (kidney failure) require either a kidney transplant or dialysis treatment to live. One form of dialysis, hemodialysis, serves to filter waste products and water from the blood—imitating the function of healthy kidneys. Before starting

hemodialysis, a surgical procedure is performed to create what is called a “vascular access,” the point at which a connection can be made to the dialysis machine, for blood to flow into the dialysis machine to be filtered and then returned to the body.



There are several types of vascular access. The arteriovenous (AV) fistula and AV graft are two types designed for long-term use. A catheter is sometimes used as a temporary means of vascular access until a longer-term form of access can be performed surgically. Vascular access has been described as the “Achilles' heel” of hemodialysis because of complications that can arise, such as infection, poor blood flow, or blockage. But for people with end-stage kidney disease, it is their lifeline—without it they cannot receive the lifesaving treatment. During each hemodialysis session, a connection is formed between the patient's blood

and the filtration machine by inserting needles through the skin into the AV fistula or graft. This process of “cannulation” is also prone to several complications (e.g., balloon-like bulge in an artery, bleeding, and clotting). Researchers are thus continuing to develop ways to improve vascular access outcomes, as well as to improve ease of use and safety as a step toward making dialysis treatment more feasible for patients to receive in their homes, rather than thrice weekly in dialysis centers.

In recent years, the NIDDK’s SBIR program has supported several vascular access technology projects to promote graft and fistula maturation. The following are examples of these projects, which are at different stages of development:

*Addressing the need to reduce clotting events, infection, and blood vessel narrowing.*

Synthetic grafts are prone to clotting events, infection, and blood vessel narrowing. This project used a regenerative medicine approach to develop a “humanized” graft (i.e., a human protein scaffolding surrounding a biodegradable polymer). In multiple clinical trials, the humanized graft was reported to be safe and functional. The small business has raised non-NIDDK/NIH capital to evaluate the product in later-stage clinical trials.

*Addressing the need to reduce needle-related complications during cannulation.*

This project developed an innovative graft that was implanted into pre-clinical models (e.g., pig and sheep) and functioned as intended with no needle-related complications reported. One version of the graft was studied in a clinical trial; then improvements were made, and a newer version is being studied in a larger trial supported by this grant. This technology could facilitate home dialysis.

*Addressing the need to improve AV fistula utilization.*

Some patients are excluded from receiving an AV fistula for lack of vessels meeting size thresholds. Prior studies have observed that patients with larger initial vein diameters have better AV fistula outcomes. Thus, there is a need to develop a system designed to rapidly and permanently dilate peripheral veins. This project developed a new technology that, when tested in sheep, doubled the diameter of veins with no adverse effects reported. A first-in-human test was then successfully completed using non-NIDDK/NIH capital.

The NIDDK will continue to pursue technologies to improve the safety and efficacy of vascular access through the SBIR program. These SBIR grants complement other NIDDK research grants to fill long-standing gaps in optimal care that are essential to ensuring the best possible hemodialysis outcomes.

Lawson JH, Glickman MH, Ilzecki M,...Niklason LE. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. Lancet 387: 2026-2034, 2016.

Gage SM, Lawson M, Nichols C, Sycks D, Manson RJ, and Knight JA. An immediate access dialysis graft designed to prevent needle-related complications: Results from the initial pre-clinical studies. J Vasc Access 21: 328-335, 2020.

Gage SM, Illig KA, and Ross JR. Use of a novel immediate access dialysis graft designed to prevent needle-related complications: A first-in-man case report. J Vasc Access 22: 475-479, 2021.



# CCEH: Increasing Collaboration and Access to Critical Research Resources for Research To Combat Nonmalignant Blood Diseases

To increase access to critical research resources, foster collaboration in blood (hematology) research, and increase the cost-effectiveness of this research, The NIDDK supports the Cooperative Centers of Excellence in Hematology (CCEH). The CCEH collaborate with the NIDDK Hematology Central Coordinating Center, collectively comprising the NIDDK Hematology Centers Program in a national multidisciplinary research effort to combat nonmalignant hematologic diseases and to study normal hematopoiesis (*i.e.*, production of blood or blood cells). The CCEH currently include five Centers, each of which involves integrated teams of investigators from a wide range of disciplines, shares specialized state-of-the-art equipment, and serves as a regional or national resource.

The Program serves as a national hub for nonmalignant hematology research by generating and providing resources and expertise to the broader research

community. In addition, the CCEH support career development of scientists in the field through national pilot and feasibility programs and local programs that fund small projects to generate preliminary data for inclusion in larger grant applications. The CCEH also sponsor short-term enrichment activities for the entire hematology research community, such as seminar series.

Examples of research areas currently under study by the CCEH include the biology of blood cells and the bone marrow niche in which blood stem cells reside, the use of blood stem cell transplantation as a potential cure for nonmalignant blood diseases, the role of iron in biological processes and its misregulation leading to deficiency or excess, and other areas.

For more information, see: <https://www.niddk.nih.gov/research-funding/research-programs/hematology-centers>.

# STORY OF DISCOVERY

## The NIDDK Provides Foundational Research Support for First FDA-approved Therapy To Treat the Metabolic Disease Primary Hyperoxaluria Type 1

### PRIMARY HYPEROXALURIA (PH)

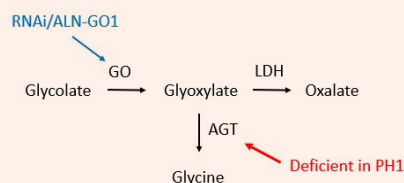
PH is a set of genetic metabolic disorders characterized by increased levels of oxalate in the kidneys, urine, and other organs of the body. The three types of PH (PH1, PH2, and PH3) are caused by a "protein deficiency" and distinguished by deficiencies in different proteins.

oxalate can build up and damage other organs, including the heart, bones, and eyes. Treatments for the disease have been limited, and the only effective treatment for most people is a combined liver-kidney transplant. The lack of effective, nonsurgical treatment options underscores the urgent need to develop new drug therapies for this serious disease.

### PRIMARY HYPEROXALURIA TYPE 1 (PH1)

- **Primary hyperoxaluria type 1 (PH1)** is a rare disorder that mainly affects the kidneys. It results from buildup of a substance called oxalate, which is normally filtered through the kidneys and excreted in the urine. In people with PH1, the accumulated oxalate is deposited in the kidneys and urinary tract and combines with calcium to form calcium oxalate—the main component of kidney stones. Symptoms of kidney stones include sudden abdominal or flank pain, blood in the urine, frequent urge to urinate, pain while urinating, and/or fever and chills.
- Indications and symptoms of PH1 vary in severity and may begin any time from infancy to early adulthood. People with PH1 may experience recurrent kidney stones, blood in the urine, and urinary tract infections. PH1 can result in end-stage kidney disease, which is life-threatening, and the need for dialysis. As kidney function worsens,

### GENETIC MECHANISMS OF PH1



- PH1 is caused by mutations in a gene called *AGXT*. This gene gives the body instructions for producing a protein called alanine-glyoxylate aminotransferase (AGT). AGT is found in the liver and converts a compound called glyoxylate to the amino acid glycine.
- Mutations in the *AGXT* gene lead to a deficiency of AGT to convert glyoxylate to glycine. This, in turn, causes glyoxylate to accumulate, and it is ultimately converted to oxalate by a protein called lactate dehydrogenase. Excess oxalate that is not excreted from the body then combines with calcium to form calcium oxalate, leading to kidney damage.

# STORY OF DISCOVERY

- The metabolic pathway leading to oxalate production includes the conversion of glycolate to glyoxylate by the protein glycolate oxidase (GO).
- Thus, glycolate oxidase is an important player in the biological mechanism leading to high levels of oxalate in PH1. Researchers discovered that targeting and thus reducing levels of glycolate oxidase using RNA interference (RNAi) technology was a promising strategy to reduce oxalate levels and treat the disease.

## THE RESEARCH PATH TO AN FDA-APPROVED TREATMENT

- The accompanying timeline shows that, for many decades, the NIDDK and the NIH have supported foundational research to better understand the metabolic dysfunction underlying PH1 (1960s), including biological pathways involved in oxalate production (1970s), development of RNAi technology to target/silence genes (1990s, 2000s), identifying glycolate oxidase as a promising target to treat PH1 (2000s), and translational research using RNAi-based approaches to target GO and reduce oxalate production in animal models of PH1 (2010s). This research laid the foundation for industry-supported trials of the RNAi therapeutic ALN-GO1 (2010s), culminating in its recent U.S. Food and Drug Administration (FDA) approval as the first drug to treat PH1 in both children and adults (2020). This decades-long story elegantly showcases how basic research elucidated biological mechanisms of both health and disease and resulted in a new therapeutic that greatly improves the prognosis of people with PH1.
- The NIDDK continues its support of this research area to improve the lives of people living with PH1 as evidenced by a recent report describing three patients with PH1 and kidney failure who were able to regain kidney function and discontinue dialysis after treatment with pyridoxine (vitamin B6).

**1963**

Studies in children showed that PH is caused by a defect in glyoxylate metabolism. (NIH Supported)

**1979**

In studies to understand how the body produces oxalate, researchers find that the liver protein glycolate oxidase converts glycolate into glyoxylate (NIH supported), and later (2004) that lactate dehydrogenase converts glyoxylate to oxalate. (NIDDK supported)

**1986**

Researchers discover that increases in oxalate, which cause PH1, result from deficiency of a liver protein called AGT. (Supported by others)

**1990**

Through genetic analysis, scientists find that people with PH1 have variants in the gene that encodes the AGT protein. (Supported by others)

**1998**

Scientists invent a novel way to target and silence a gene of interest so that the protein it encodes is not produced. They subsequently win the Nobel Prize. This research would prove transformative for many areas of research—including later development of a treatment for PH1. (NIH supported)

**2008**

Research suggests that approaches that target glycolate oxidase may prove useful for decreasing glyoxylate levels and subsequent oxalate production in PH1. (NIDDK supported)

**2016**

Data collected via a patient registry of all forms of PH showed that higher urinary oxalate excretion is associated with end-stage kidney disease. (NIDDK supported)

**2016**

Investigators show that RNAi targeting liver glycolate oxidase reduced oxalate production in a mouse model of PH1, suggesting that RNAi therapy may be a promising approach for treating people with PH1. (NIDDK supported)

**2017**

Researchers report that an RNAi therapeutic called ALN-GO1 targeting liver glycolate oxidase decreased oxalate production in healthy mice, rats, and non-human primates, and up to 98 percent in a rat model of PH1. (NIDDK supported)

**2018**

Building on NIDDK-supported research on ALN-GO1, industry-supported clinical trials evaluate the efficacy and safety of this potential RNAi therapeutic in children and adults with PH1. (Industry supported)

**2020**

FDA approves use of RNAi therapeutic ALN-GO1, which targets liver glycolate oxidase, as first treatment for PH1 in both children and adults.

## Helping People Hydrate To Prevent Kidney Stones

Kidney stones are a common ailment in the United States. Most kidney stone research and treatments to date have focused on helping people who have a kidney stone and are having excruciating pain; more research is needed about how to prevent and effectively manage kidney stones. The NIDDK is currently supporting a clinical trial that hopes to identify ways to change behavior so a person is less likely to have another kidney stone, and help determine if drinking more water can help prevent kidney stone recurrence. As behavior change is not always easy—especially in times of challenge such as the current COVID-19 pandemic—teamwork, support, and flexibility among study volunteers, staff, and investigators have been especially important to successfully moving this important research forward. (See insets for perspectives on the clinical trial from study coordinators.)

### WHAT ARE KIDNEY STONES?

A key function of the kidneys is to filter out toxins and waste products from the blood. Together with water and salt, this filtration process forms a waste liquid called urine, which is sent to the bladder for storage and then expelled via urination (“peeing”). However, solid deposits can develop when there is a high concentration of certain minerals and salts in the urine. Commonly referred to as kidney stones, clinicians and scientists also use the term “urinary stone disease” for this phenomenon because although most often initiated in the kidney, these deposits can form and/or cause problems almost anywhere in the urinary tract. Kidney stones vary in size, shape, and type. Quite often people have them and pass them out of the body without knowing it or without an intervention. However, kidney stones can also get stuck in the kidneys or in the tubes, called ureters, that carry urine to the bladder. This can cause severe pain and/or bleeding, frequently sending people to the emergency

room for care. The prevalence of kidney stones has nearly doubled in the past 15 years, and current estimates are that 1 in 11 people in the United States is affected. Kidney stones are more common in men than in women, but they are increasingly occurring in younger women, and they can also occur in adolescents and youth. Importantly, persons who have had a kidney stone in the past are more likely to have another.

Advances in treatment, such as using targeted high energy shock waves to blast larger stones into small pieces that can be passed more easily, means that some stones can be treated noninvasively. There are also some medicines available to help prevent recurrence of specific types of stones. However, not all treatment is noninvasive or fully effective. In fact, the majority of symptomatic kidney stones are treated using a surgical procedure in which a thin, flexible telescope is inserted into a ureter to help the doctor either snare a stone directly or use a tiny laser to fragment it for subsequent removal or natural passage, often accompanied by temporary placement of a small tube (stent) in the ureter to help with drainage. Moreover, estimates indicate that urinary stone disease is one of the costliest urologic conditions. Thus, a double-pronged approach focusing on both prevention and therapeutics is necessary.

### THE URINARY STONE DISEASE RESEARCH NETWORK

To address the burden that kidney stones place on people and the health care system, in 2016 the NIDDK funded a coordinating center and four clinical centers across the country to form the collaborative Urinary Stone Disease Research Network (USDRN). USDRN scientists are designing and conducting research on kidney stones in adults and children to learn more about who is at higher risk for kidney stones, symptoms



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associated with the placement of stents in a ureter, and how to prevent stones from forming again. By developing a robust evidence base, it is hoped that USDRN studies will provide a foundation for novel approaches and management strategies for kidney stones and their prevention.

There are several factors associated with the development and recurrence of kidney stones, but one of the main risk factors is inadequate hydration. This leads to low daily urine volumes and thus higher salt and mineral concentrations. Evidence suggests that significantly increasing fluid consumption to produce 2.0 to 2.5 liters (about 8.5 to 10.5 cups) of urine daily can prevent or delay recurrence of kidney stones, and would be a low risk, inexpensive, and effective approach. However, although people who have had kidney stones are commonly counseled to increase their fluid intake, this can be challenging for many reasons. These range from simple forgetfulness to limited bathroom access to having other urinary symptoms that cause hesitancy about drinking more fluids. Another reason is that it is easy to lose sight of how helpful a behavioral change can be once an immediate health crisis—such as severe pain from passing a stone—has ended. As a result, not many people who have had a kidney stone end up increasing their fluid consumption significantly.

In light of these challenges, the USDRN developed and launched a clinical trial to test a strategy that could help people who have had at least one kidney stone effectively increase and maintain their fluid intake and prevent stone recurrence. This trial is called the Prevention of Urinary Stones with Hydration, or PUSH.

## THE PUSH CLINICAL TRIAL: A NOVEL APPROACH TO INCREASING HYDRATION

PUSH is a randomized clinical trial testing the effectiveness of a multi-component behavioral strategy to increase water intake and consequent urine output enough to prevent kidney stone recurrence in adolescents and adults. PUSH has enrolled volunteers ages 12 and older with a history of stones, daily urine

output lower than the study target, and who own a smartphone or tablet they are willing to use for the study. The trial set an enrollment goal of 1,642 people, which it expects to meet in early 2022.

Once enrolled, a PUSH participant is randomly assigned into one of two groups for a 2-year follow-up period: the usual care “control” group or the intervention group. In both groups, participants are given a commercially available “smart” water bottle that tracks water consumption through a smartphone or tablet app. Participants in the usual care group receive standard recommendations to increase their overall fluid intake in order to achieve daily (24 hour) urine output of at least 2.5 liters or, for adolescents weighing less than about 165 pounds, an increase in urine output scaled to their weight. They are allowed but not required to use the smart water bottle to help monitor their water intake. They also receive monetary compensation for completion of study activities.

Participants randomly assigned to the PUSH intervention group receive usual care information and have the same urine output targets, but they are also engaged in a three-pronged behavioral change program intended to help achieve and maintain the targets, consisting of the following:

- They are provided with individualized, calculated “fluid prescriptions” indicating the additional amount of water they need to consume daily via the smart water bottle to achieve the PUSH target urine output; this water is in addition to any other fluids they normally consume.
- They are provided small financial incentives for meeting their daily water goal, set up as a banked total amount each month in which the incentive available on a particular day is lost if a goal is not met; participants are notified about whether they’ve kept or lost incentives via encouraging text messages. The incentive is available every day at the beginning of the trial, but is then tapered down in phases, such that during the last 6 months of the trial there is no longer a financial incentive.

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- In parallel, during year 1, they are provided access to health coaches and structured problem-solving sessions and “boosters” to help overcome individual barriers to meeting fluid intake goals. Participants who still have challenges with adherence to their fluid goals after year 1 have access in year 2 to alternative, “low touch” interventions that they select themselves, such as text or telephone reminders or engaging a support partner.

At the end of the trial, PUSH researchers will compare data from the two groups regarding the number and timing of symptomatic stone events as defined by the study. This way, they can determine whether or not the structured, phased, behavioral change intervention provides a significant benefit over usual care by preventing or delaying recurrence of stones that either induce symptoms and/or require medical intervention.

According to the original study design, during the 2 years a person is enrolled, all participants are also asked to perform periodic 24-hour urine collections at home, have kidney imaging performed at the beginning and end of their participation, and fill out online questionnaires about general health status and their stone disease every 3 months, and, for adult participants, questionnaires about urinary symptoms every 6 months. These measures can provide insights into changes in urine output as a result of the intervention, changes in preexisting stones present in the kidney, and how the intervention affects urinary symptoms.

## COVID-19 AND PUSH: KEEPING IT GOING

The PUSH clinical trial began in September 2017. In March 2020, the COVID-19 pandemic led to an abrupt shutdown of laboratories and clinical trials, as new safety measures were put in place to protect investigators, study volunteers, and others involved in or supportive to the biomedical research enterprise. At that time, just over half of the anticipated volunteers had been assigned to an arm of the PUSH clinical trial.

In response to COVID-19, the USDRN rapidly developed a plan to restart PUSH in a way that would enable continued recruitment of volunteers while keeping both them and study personnel safe. This included considering how to lower barriers to participation and retention, especially as people might be hesitant to join a clinical study in person or undergo in-person procedures, such as imaging. In consultation with the trial’s Data Safety Monitoring Board and working with the Institutional Review Boards at each clinical site—all of which have a role in ensuring clinical trial participant safety and welfare—the PUSH clinical trial received approval for remote recruitment. This includes obtaining informed consent by phone or video, enrolling participants, and randomly assigning them to one of the two trial groups.

As a result, the PUSH trial not only implemented a change to make consenting processes safer and easier for potential participants and staff, but it leveraged this change to reach out and recruit participants from across the Nation. This lack of geographic barriers is enabling PUSH to enroll a more diverse population. It has also formed partnerships with health care systems—in particular, pediatric kidney stone care systems, which has accelerated identification of adolescents interested in joining PUSH. The USDRN also determined that PUSH had sufficient data from already enrolled patients to enable them to waive other in-person requirements, such as on-site kidney imaging procedures at enrollment and/or close out, and instead would use as possible images and other data obtained during regular clinical care going forward. What the USDRN learned from necessity, and the flexibility it added due to COVID-19, may serve as a model for design of other clinical trials.

## COORDINATING FOR SUCCESS

During the PUSH study—and, indeed, during most clinical trials—volunteers interact with a variety of trial personnel, but a common face is that of the study coordinator. Study coordinators, or clinical research coordinators, are linchpins in a clinical trial. Their wide array of responsibilities includes helping recruit and

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enroll study volunteers, serving as liaisons with study investigators and the research institution, monitoring progress and maintaining all required forms, ensuring compliance with all regulations, preparing reports, and being a key point of contact for study volunteers throughout the duration of a clinical trial—a role that is often crucial to helping participants see a study through to the end in the midst of busy lives, responsibilities, and other challenges.

In a behavioral change study such as PUSH, in which participants know whether they are in the intervention or the control group, study coordinators are also critical to helping keep the study “blinded” to most of the staff and to participants’ health care providers. That is, it is crucial that study investigators, clinicians, treatment providers, and the statisticians who analyze the study results have no idea about who has been assigned to which study group, or about certain individual characteristics—that way, there is less risk of biased actions occurring during the trial, analyses of data, and in the interpretation of results.

Thus, PUSH study coordinators are key go-betweens. Study coordinators also get to see firsthand the challenges that volunteers may be having in adhering to trial requirements, and also help them in navigating these challenges so that they are more likely to complete the trial successfully. In a study such as PUSH, the challenges that arise toward achieving the goals of the intervention can also be different for youth and adults.

The additional challenges imposed by COVID-19 have also meant increased training for PUSH staff and new strategies and flexibility for them and for study volunteers. Yet, together, they are coordinating for ultimate success of the PUSH trial and its goal of determining whether a behavioral change strategy focused on increased hydration can indeed help people avoid recurrent kidney stones and the associated pain, life disruption, and burden of care.

*To learn more about the PUSH trial, see:*  
<https://usdrn.org/participate/push>.

## BRITTNEY’S EXPERIENCE AS A PUSH STUDY COORDINATOR



Brittney

Brittney, 29, grew up in Georgia and describes herself as both a quiet lover of books and an avid sports fan, especially football. She laughs as she says she has found herself “screaming at the television” when rooting for her favorite teams, the Philadelphia Eagles and the University of North Carolina Tar Heels. Adding that she is “an introvert, but enjoys working on great teams,” she shared her experience as a research study coordinator for the University of Pennsylvania/Children’s Hospital of Philadelphia, or CHOP. Brittney joined the Prevention of Urinary Stones with Hydration, or PUSH, clinical trial team at CHOP in March 2017, shortly after completing her master’s degree in public health. CHOP soon

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enrolled its first PUSH trial participant from among kids 12 and older, in October 2017. Brittney remembers how the first enrollments took “an hour and a half, and the patients were all so nice!” as everyone got through the process together, from reviewing how to use the smart water bottle to going for imaging in other parts of the medical complex. Later, she generally worked with three to four participants per day who were at various stages in the trial. To facilitate the study and make participation easier, she constantly sought out ways “to prevent having any barriers or burdens ... on the parents as much as possible,” such as coordinating kids’ research and clinical appointments at CHOP well in advance.

*Brittney, a study coordinator for the PUSH clinical trial, constantly sought out ways “to prevent having any barriers or burdens ... on the parents as much as possible” to facilitate the study and make kids’ participation easier.*

Brittney keenly remembers the rapport she and participants built during their initial visits, which helped kids and their families throughout their time in the trial. They felt comfortable texting her with questions and asking for help related to study activities. She did a lot of listening and problem-solving, saying that probably the biggest frustration for kids and families was when they felt they were doing everything right, but for some reason the bottle “just would not work.” Another challenge for some was wanting to keep life simple and use just one bottle for all their drinks, whereas for kids in the PUSH intervention group the smart water bottle was meant to provide a prescribed amount of supplemental water per day. “We really tried our hardest to make sure we could compromise where we could, and let them know where we couldn’t,” says Brittney. It was also super important to make

sure that kids as well as parents were on board with the study, she says, noting that, “one of our big points [when enrolling someone] was that ‘this was one of the things you have to want to do for yourself, because it is supposed to be a behavior change.’” Along these lines, she adds that although kids might not always have been excited about getting automated daily messages to help with behavior change, it was “funny ... how quickly they would respond” if they got a message saying that they had missed out on the financial incentive when they knew they had met their hydration goal—and, of course, she would fix it for them.

When the COVID-19 pandemic temporarily halted PUSH recruitment in early 2020, Brittney took on double duty, becoming part of the COVID-19 clinical volunteer team at CHOP while continuing to send materials and make remote calls to support kids already enrolled in PUSH. As PUSH reopened and there was approval for remote recruitment, Brittney began contacting potential new participants by phone. She continued strategizing to keep participation easy, appealing, and safe in light of COVID-19-related uncertainties and fears—including letting families know when procedures or samples they needed for kids’ clinical care could be done and covered as part of their PUSH participation, and reassuring worried parents that their kids could now opt out of end of study kidney imaging. Brittney left CHOP in July 2020 to enroll in medical school back in Georgia, noting that she still “loves urology” and is hoping to pursue a career in surgery. She remembers with deep appreciation how some of the families told her at the end of their participation how the time and care she took with them “really changed their lives.” From her time at CHOP and the PUSH study, particularly as they faced the pandemic, she says she remains inspired by the kids and families with whom she met and worked. How to capture her feelings in one word? “Resilience,” says Brittney.



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## HOLLY'S EXPERIENCE AS A PUSH STUDY COORDINATOR

Seattle area native and mother of two, Holly, 41, has been a clinical research study coordinator for over 14 years—4 of them with the Prevention of Urinary Stones with Hydration (PUSH) clinical trial site at the University of Washington (UW), which is enrolling adult participants. When not spending time with her sons at Mariners Stadium and other activities as the COVID-19 pandemic allows, she is mainly focused on her study coordinator role, a career that she says she “fell into” and trained for while working at a private practice, and found she really enjoys. Along with data collection and administrative aspects, “I enjoy the volunteers’ participation and ... face-to-face contact [with them],” she says with a smile. On a daily basis, Holly spends much of her time determining whether potential PUSH participants meet eligibility criteria for the study, going over the study with eligible candidates so they are fully informed prior to joining, and randomly assigning new participants to one of the two PUSH study groups. She does this either in person or now also remotely, including people from across the country. So far, “we’ve had success enrolling people from Oklahoma, Tennessee, and New York,” as well as Arizona and



Holly

California, she says. Because the PUSH trial didn’t require in-person visits for most of a participant’s involvement even before the pandemic, Holly adds that “we were already comfortable helping people along the way for 2 years remotely,” including with

issues such as smart water bottles breaking or the associated tracking app not working.

Holly emphasizes that a big goal for her and the rest of the PUSH team is to make sure participants do not feel burdened by the study, but rather feel it is something they can integrate into their daily lives. “Being a prevention study, we want it to be a positive experience for them,” she says. As part of the study, she often reaches out to participants to help with their 3-month follow ups as needed, but also hears about their frustrations at other times, such as when they don’t meet hydration goals. “Sometimes people just had to take a break,” she says, adding that when she randomizes participants she makes sure to let them know that, “we understand life gets busy and, yes, you can’t meet your goal every day, but we are here to help you.”

Holly has found that, despite some of the frustrations they encounter, the PUSH participants she has worked with are really positive about their experience. She says that most of the people who volunteer for PUSH “are very excited to start the study,” adding that “one of the best things is that ... at the end of their 24 months, they are really proud of themselves” regarding improvements in 24-hour urine collections and water consumption, and “that’s always good to see.” She observes that they know that not only are “they helping themselves, but also really contributing to kidney stone disease” research. In terms of their daily experience, she says that participants in the intervention group “really [do] love the smart water bottle” and being able “to see where they [are] at during the day for their goal” and whether they’ve met it, via the app. Participants are allowed to keep their bottles at the end of their study time, and Holly says a few have said at that point that

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they are “sad that they weren’t able to continue on” in PUSH, although of course they can continue to use the bottle to monitor water consumption.

*Holly, a study coordinator for the PUSH clinical trial, emphasizes that a big goal for her is to make sure participants do not feel burdened by the study: “Being a prevention study, we want it to be a positive experience for them.”*

For Holly, as the PUSH clinical trial continues its work through the evolving challenges of the COVID-19

pandemic, teamwork and support are critical—both personally and for the participants. It’s “not only us trying to be positive and supportive,” but also, “here at the clinical site we have support from the principal investigators, ... the monitors, and the coordinators [and assistants] supporting each other during this difficult time,” she says. She was especially thankful for this support when dealing with wildfires near her home in 2020. Talking again about the study volunteers, Holly recalls fondly how one participant even gave the UW PUSH team the moniker “Team Hydrate.” This seems to capture the spirit of PUSH—go Team Hydrate!