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Kidney, Urologic, and Hematologic Diseases

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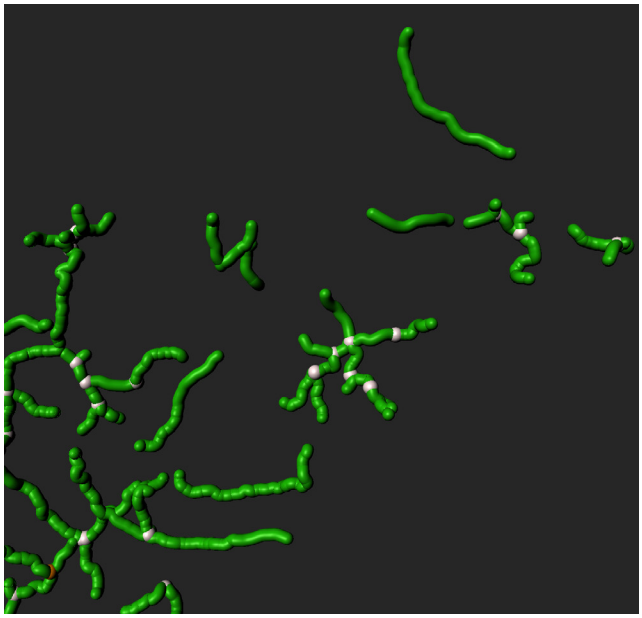

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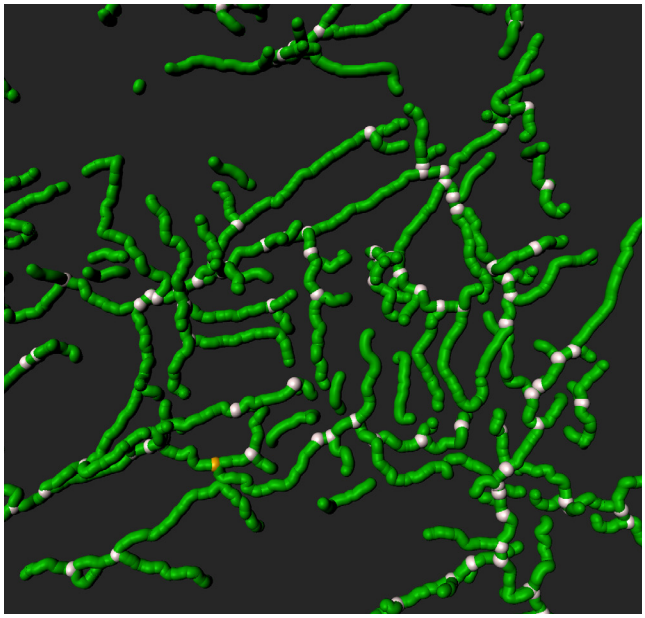

RECURRENT UTI

Pelvic pain is a significant component of many urologic diseases. For example, people who experience recurrent urinary tract infections (UTIs) often continue to experience symptoms such as pain and increased urinary frequency even after the infection has cleared—a phenomenon that is poorly understood. Described in this chapter are findings from a recent study revealing that increased nerve growth and sprouting in the bladder may be a major contributor to lasting pain symptoms experienced by people who frequently develop UTIs. This image depicts a three-dimensional model of the increased nerve sprouting (green fibers) observed in the bladders of mice that were given three consecutive UTIs (right) compared to the bladders of healthy mice (left). This increased level of nerve growth could explain why pain and voiding defects persist after an infection has been cleared and may help lead to new therapeutic approaches.

From: Hayes BW, Choi HW, Rathore APS,...Abraham SN. Recurrent infections drive persistent bladder dysfunction and pain via sensory nerve sprouting and mast cell activity. Sci. Immunol 9: eadi5578, 2024. Reprinted with permission from AAAS.

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, 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 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 35.5 million American adults have impaired kidney function—also called chronic kidney disease (CKD).[1] However, up to 9 of every 10 adults with CKD are not aware that they have the disease.[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 more 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 35.5 million American adults have chronic kidney disease.

CKD, especially if undetected, can progress to irreversible kidney failure, a condition known as end-stage kidney disease (ESKD). People with ESKD require dialysis or a kidney transplant to live. In 2021, over 808,000 patients in the United States and its territories were living with ESKD.[2] Over 556,000 received either hemodialysis or peritoneal dialysis, and over 251,000 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 ESKD. ESKD prevalence in 2021 was about four times greater in African Americans; over twice as high in American Indians, Alaska Natives, and Hispanic Americans; and almost 1.6 times greater in Asian Americans, compared to Whites.[2] NIDDK supports a significant body of research aimed at understanding the biology underlying CKD and developing treatment strategies.

In addition to research on kidney disease related to diabetes and high blood pressure, 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. One feature common to kidney diseases arising from varying causes is the deposition of fibrotic scar tissue in the kidney. Research supported by 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.

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[1] *Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2023. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2023.*

[2] *United States Renal Data System. 2023 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, 2023.*

Urologic diseases and conditions affect people of all ages, result in significant health care expenditures, and can lead to substantial disability and impaired quality of life. Areas of NIDDK-supported research 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 (UI) is another prevalent problem. Based on U.S. medical insurance claims over several years, the annual prevalence of UI among individuals 65 and older enrolled in Medicare fee-for-service plans ranged from 7.0 to 7.8 percent for women and from 3.6 to 4.0 percent for men. Among privately insured women aged 18 to 64, prevalence was approximately 1.1 percent compared to 0.2 percent for men.[3] These estimates may be lower than the actual prevalence of UI due to stigma surrounding the condition. Many suffer in silence due to embarrassment and lack of knowledge about treatment options available.

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 kidney disease.

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 large, national interview survey conducted from 2007 to 2009, it was estimated that among U.S. women 18 years or older, about three to eight million have pelvic pain and other symptoms, such as urinary urgency or frequency, that are associated with IC/BPS.[4] Using a community-based epidemiologic survey, researchers estimated that among U.S. men ages 30 to 79 years old between 2002 and 2005, 1.3 percent had persistent urologic symptoms, such as pain with bladder filling and/or pain relieved by bladder emptying, that are associated with IC/BPS.[5] 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.

Research on UCPPS is one example of how NIDDK is seeking a broad-based understanding of lower urinary tract symptoms (LUTS), including pain, bladder leakage, and problems urinating. For the wide range of LUTS, we still need to learn more about causes and contributing factors to improve management and treatment of symptoms. NIDDK is supporting research to better understand factors that contribute to bladder health over the lifespan, with the ultimate goal of preventing LUTS.

Among U.S. women 18 years or older, about three to eight million were estimated to have pelvic pain and other symptoms, such as urinary urgency or frequency, associated with interstitial cystitis/bladder pain syndrome.

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. 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.

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[3] *Urologic Diseases in America. 2024 UDA Data Report: Epidemiology of non-malignant urologic disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2024.*

[4] *Berry SH, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 186: 540-544, 2011.*

[5] *Link CL, et al. Prevalence and psychosocial correlates of symptoms suggestive of painful bladder syndrome: results from the Boston Area Community Health (BACH) survey. J Urol 180: 599-606, 2008.*

INVESTIGATING FACTORS INVOLVED IN KIDNEY DISEASE PROGRESSION AND OUTCOMES

Three-Dimensional Map of Kidney Cell Activity Reveals Importance of Fibrosis in Disease Progression: Researchers identified molecular signals of fibrosis that predict chronic kidney disease progression through methods that map individual kidney cells in three dimensions and analyze gene activity in the cells. Healthy kidneys contain an intricate array of complex structures called nephrons, which constantly filter the blood and concentrate waste in urine. Nephrons, and the tissues surrounding them, are made up of dozens of well-defined cell types, each with specific roles in kidney function. This nephron system is damaged, over time, by the most common causes of chronic kidney disease (CKD) in adults: hypertension (also known as high blood pressure) and type 2 diabetes. In both cases, CKD is associated with fibrosis—essentially a process in which normal tissue is replaced by scar tissue. The role of kidney fibrosis—whether it is a cause or a symptom of disease progression, for example—has been a matter of debate.

Newly identified molecular signatures of kidney fibrosis may indicate progressive kidney diseases even when physical signs of fibrosis are not yet evident.

Scientists have developed a variety of cutting-edge methods to analyze the gene activity within individual cells. Each of these methods has differing strengths and weaknesses, so researchers combined approaches, dramatically extending what was known about the molecular activity within different kidney regions—allowing insights about changes that signal progression to kidney disease. They analyzed the activity of individual cells in kidney biopsy samples from donors who were healthy or who had some degree of fibrosis associated with CKD caused by either hypertension or diabetes. Because fibrosis does not develop uniformly in CKD, they repeated this analysis on hundreds of thousands of kidney cells, allowing them to determine what was occurring in specific cell types of individual nephrons throughout the kidney. This approach allowed them to identify a molecular signature distinguishing cells from fibrotic or non-fibrotic regions, regardless of cell type. They then analyzed cell samples from 292 donors who were healthy or had varying severity of CKD caused by hypertension or diabetes, but in whom the degree of fibrosis was unknown. The fibrotic signature correlated strongly with severity of CKD. Importantly, by looking for this signature in cells collected from the same donors at various times, the scientists showed it was a potent predictor of CKD progression—even in cases where a pathologist was unable to see marked physical signs of fibrosis.

Thus, detectable molecular events leading to fibrosis occur early in CKD. Collecting kidney cell samples is an invasive procedure that comes with some risk, and this complex analysis needs to be confirmed through further research. For these reasons, this method is unlikely to be developed soon into a widely available diagnostic approach for predicting CKD outcomes. However, these findings do indicate that such an approach could one day be possible and suggest it may be worth adapting therapeutics targeting fibrosis in other tissues to investigate their potential for slowing CKD progression.

Abedini A, Levinsohn J, Klötzer KA,...Susztak K. Single-cell multi-omic and spatial profiling of human kidneys implicates the fibrotic microenvironment in kidney disease progression. Nat Genet 56: 1712–1724, 2024.

Newly Discovered Markers of Risk for Chronic Kidney Disease Progression: Recent research has identified dozens of proteins that are found at significantly different levels in the plasma of people with chronic kidney disease (CKD) that worsens more rapidly than in people with relatively stable kidney disease. Progression of CKD is associated with a high risk not only for kidney failure, but also for complications including cardiovascular disease, bone and metabolic disease, and frailty. The likelihood that a person will experience a significant decline in kidney function over 10 years can be calculated using a "kidney failure risk equation" (KFRE), which factors in their age, sex, current estimated kidney function, and urine levels of a protein called albumin. However, the KFRE does not provide clues about what might cause CKD progression in individual cases. In addition, the components of the KFRE are not modifiable in a way that might prevent progression. For these reasons, scientists want to improve on the KFRE by developing a method that can highlight potential causes of CKD progression and even suggest new ways to stop it.

Researchers have newly identified dozens of protein biomarkers that may help predict a person's likelihood of progressing to severe chronic kidney disease.

Accordingly, they measured the levels of more than 4,500 proteins in plasma samples from more than 3,000 people with CKD who participated in the NIDDK-supported Chronic Renal Insufficiency Cohort study. They identified specific proteins that tended to be present at significantly higher or lower levels in participants whose kidney function declined by half over a 10-year period than in those whose CKD remained relatively stable. The researchers then tested the findings from this initial analysis using samples from participants in the Atherosclerosis Risk in Communities study: 100 such proteins turned out to be significantly associated with CKD progression in participants from both studies. The researchers created a panel of 65 of these proteins that provides about the same power to predict the 10-year risk of CKD progression as the KFRE and has even better predictive power at 5 years. If these results are confirmed, it may one day be possible for clinicians to improve on their ability to distinguish people with CKD whose progression risk is particularly high and who might therefore benefit from more aggressive therapy and monitoring. The study scientists also found evidence that 14 of the proteins in this panel are potential targets for medications that could one day slow or stop the decline in kidney function. Additional research will be needed to design and test such therapeutics to determine if they can safely prevent CKD progression.

Dubin RF, Deo R, Ren Y,...Ganz P; for the CRIC investigators and the CKD Biomarkers Consortium. Proteomics of CKD progression in the Chronic Renal Insufficiency Cohort. Nat Commun 14: 6340, 2023.

Many Genes Can Affect the Outcomes of Kidney Diseases Caused by Variations in Single Genes:
Researchers have found that when people have a genetic variation that causes either autosomal dominant polycystic kidney disease (ADPKD) or a form of Alport syndrome (*COL4A*-associated nephropathy, COL4A-AN), their likelihood of developing chronic kidney disease (CKD) is significantly influenced by the variants they carry in other genes. CKD is common and can occur for many reasons, but some genetic diseases greatly increase the chances of developing CKD. The most common form of inherited kidney disease, ADPKD, is usually caused by variants in either of two genes. However, ADPKD severity varies substantially even among people who have the same, specific versions of these genes; and in some cases, they might never go on to develop CKD at all.

Scientists recently developed an approach to calculate the risk of CKD in people without known genetic kidney diseases. By looking at common variations in dozens of genes, they developed a "polygenic risk score." CKD risk was then assigned based on these scores, with people in the middle third of the scoring range having average risk, those in the bottom third having lower risk, and those in the highest third having higher risk. In the new research, they applied this same polygenic risk formula to people with known ADPKD-causing variants, utilizing data from cohorts from the UK Biobank and NIH's *All of Us* Research Program. Compared to the average CKD–risk group of people without ADPKD, people with ADPKD variants who are in the lowest third of polygenic risk have a 3-fold higher likelihood of developing CKD, those in the middle third have a 36-fold greater risk, and people with ADPKD variants who are in the highest third of polygenic risk have a 54-fold higher likelihood of developing CKD. For people with genetic variants that cause COL4A-AN, being in the highest risk group was associated with 2.5 times the CKD risk than being in the middle third of the group without known CKD-causing variants, while being in the lowest third was not associated with significant additional risk for CKD.

New research may one day help people with genetic variants that cause certain kidney diseases assess their risk of progressing to chronic kidney disease.

The polygenic risk score was developed with samples from participants in a large, predominantly White European study but was replicated with samples from a more diverse (57 percent non-White) group of study participants. Still, the researchers noted that their approach had lower predictive power in non-White individuals, and further research will be needed to address this problem. If confirmed, this approach could help individuals with kidney disease-causing genetic variants—or their parents—assess their risk of progressing to CKD.

Khan A, Shang N, Nestor JG,...Kiryluk K. Polygenic risk alters the penetrance of monogenic kidney disease. Nat Commun 14: 8318, 2023.

EXPANDING KNOWLEDGE OF INJURED KIDNEY CELLS

Y Damage Happens: Loss of Y Chromosome Observed in Injured Kidney Cells: Scientists have found that increased loss of sex-specific DNA in kidney cells is associated with kidney injury and could serve as a marker of chronic kidney disease (CKD) progression. Chromosomes are structures within cells that neatly organize DNA, with sex chromosomes determining whether a person is biologically male (one X and one Y chromosome) or female (two X chromosomes). Canonically, all cells in an organism have the same chromosomes; however, errors in cellular replication can lead to differences over time. Males can lose the entire Y chromosome from some cells—called mosaic loss of Y chromosome (LOY)—which has been associated with aging and certain diseases.

To understand if LOY occurs in people with CKD, scientists utilized cutting-edge technologies to determine the presence of Y chromosomes in different types of kidney cells from people that had CKD and those that did not. Combining this information with previously published data to make the results more robust showed that the kidney cells most prone to injury also had the highest chance for LOY. LOY was accompanied by other changes in cells, including altered levels of proteins that turn certain genes on and off, changes in the likelihood that the cell will replicate, and an increased likelihood they produce pro-inflammatory molecules that can ultimately lead to tissue scarring and damage. The scientists found that LOY frequency also increased with age and that LOY was a risk factor for further DNA damage. More research will be needed to understand whether LOY or cellular injury occurs first, but the presence of DNA damage like LOY may serve as a marker of kidney disease progression that could be readily detectable from human kidney biopsies.

This work is part of a larger NIDDK effort termed the Kidney Precision Medicine Project (KPMP) that seeks to better understand the mechanisms of kidney injury and define disease heterogeneity. DNA damage is just one component of a larger mechanistic picture observed with reduced kidney function, but understanding it could lead to new approaches for CKD treatment or prevention.

Wilson PC, Verma A, Yoshimura Y,...Humphreys BD. Mosaic loss of Y chromosome is associated with aging and epithelial injury in chronic kidney disease. Genome Biol 25: 36, 2024.

INVESTIGATING KIDNEY HEALTH IN SPACEFLIGHT

"Cosmic" Kidney Disease—How Extended Spaceflight Can Cause Kidney Problems: New research is shedding light on the kidney-health risks people may experience during extended spaceflight. While in space, astronauts experience weightlessness, which has well-documented consequences on the musculoskeletal system, such as loss of bone mineral density and decreased muscle mass. Another well-documented effect of spending time in space is a dramatically increased risk for kidney stones—also known as urinary stone disease—and one plausible explanation is that the minerals lost from bone are ending up in the stones. However, there are numerous environmental differences between living on earth and travelling in space that might affect health and could be involved in stone formation. Since a urinary stone experienced during, for example, a journey to Mars—on the surface or during the return—could require emergency surgery (a procedure that might present its own challenges in the absence of gravity), planning for such exploration necessitates understanding what causes kidney stones in spaceflight and how to reduce their likelihood or prevent them.

To address these concerns, researchers examined samples from astronauts and animals that had experienced real or simulated low-orbit spaceflight. These samples included blood and plasma collected from 86 people (mostly male) before, during, and/or after spaceflights lasting from 3 to 199 days. The samples showed chemical changes consistent with elevated risk for urinary stone formation. Importantly, the study found that in addition to bone loss, other factors—including the relatively high levels of radiation experienced by travelers who leave earth's protective magnetic field—are likely contributing to the physiological changes and kidney dysfunction they observed. Radiation exposure is expected to be a much greater concern for travelers exiting the partial protection of low Earth orbit, for example during hypothetical journeys to Mars. By mapping the chemical and structural changes occurring in kidneys exposed to spaceflight, the researchers were able to suggest potential therapeutic approaches (such as maximizing fluid intake and taking certain medications) that might help limit the danger of stones and other kidney diseases. Further research will be needed to determine whether any of these therapies will be safe and effective during spaceflight.

Siew K, Nestler KA, Nelson C,...Walsh SB. Cosmic kidney disease: an integrated pan-omic, physiological and morphological study into spaceflight-induced renal dysfunction. Nat Commun 15: 4923, 2024.

ASSESSING PAIN IN UROLOGIC CHRONIC PELVIC PAIN SYNDROME

Better Assessment of Pain Associated With Bladder Filling in People With Urologic Chronic Pelvic Pain Syndrome: Scientists have developed a simple, yet effective, assessment for pain upon bladder filling and reported the neurological impact of this pain in people with urologic chronic pelvic pain syndrome (UCPPS). UCPPS, which is a collective term for both interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, is defined by chronic pain in such areas as the pelvis, urogenital floor, and external genitalia. The pain symptoms experienced by people with UCPPS are typically self-reported, and studies have shown that only a subset of people experience pain with bladder filling as a symptom. This fact, coupled with a lack of adequate tests for pain-related symptoms, makes it difficult to determine the most effective treatment strategies for people with these conditions.

Researchers developed a new clinical test of bladder-filling pain in people with urologic chronic pelvic pain syndrome.

The NIDDK-sponsored Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network's Symptom Patterns Study is an observational study to better understand the long-term changes in pelvic pain symptoms among people with UCPPS. As part of this study, researchers administered a bladder-filling assessment to 429 people with UCPPS. Study participants consumed 12 ounces of water after initial emptying of their bladder and then reported their pain levels 20 and 40 minutes later. Immediately following the bladder-filling test, participants also underwent a 10-minute MRI to observe and collect images of their brain structure and activity. With this baseline assessment and a subsequent 6-month assessment, the researchers identified two primary bladder-filling pain subtypes, with those designated as bladder-filling pain negative (BFP-) experiencing the lowest pain levels and bladder-filling pain positive (BFP+) experiencing the highest. They discovered that when compared to BFP- people or healthy controls without UCPPS, the brains of BFP+ participants showed increased functional activity in brain areas associated with sensory and pain processing during bladder filling. They also observed that a BFP+ result was better than self-reported bladder-filling pain assessments at helping predict long-term factors like symptom flare-ups or necessary changes in medication for up to 18 months post-baseline assessment.

This study highlights the value of developing a standardized, natural test that can more consistently observe bladder pain symptoms that are sometimes difficult to characterize via self-reporting. If future studies find this tool to be useful in a broader population, it could aid in more accurate clinical diagnoses and treatment recommendations for people with UCPPS and bladder-filling pain.

Schrepf AD, Mawla I, Naliboff BD,...Kutch JJ. Neurobiology and long-term impact of bladder filling pain in humans: a Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network study. Pain 164: 2343-2351, 2023.

STUDYING URINARY TRACT INFECTIONS

Characterization of Catheter Microbial Communities to Improve Urinary Tract Infection Treatment: By detailing the bacterial communities that form on long-term catheters, researchers provided important insights toward better treatment strategies for catheter-associated urinary tract infections. While urinary catheters may be used for days or weeks while tissues heal after surgery or treatment of urinary blockage, in some cases they are used long term and require periodic replacement. The risk of infection from bacteria that has entered the body and grown on the catheter increases with long-term catheter use. Catheter-associated urinary tract infections are a common health care–associated infection and are responsible for increased morbidity and mortality, lengthened hospitalizations, greater costs, and antimicrobial use that can promote antibiotic resistance.

To characterize the composition of the microbial communities associated with long-term catheter use, the researchers collected bacterial samples from the catheters and urine of non-hospitalized people when they came in to have their catheter replaced. On average, participants had their catheters replaced every 30 days, so the researchers were able to collect samples monthly for up to a year. Analyses revealed a total of 88 different species of bacteria in the samples with

an average of two to three unique species in a single collection from an individual and six different species across all collections from an individual. Even though over 70 percent of the participants received at least one course of antibiotics during the study, bacteria persisted in most samples and, in one participant, became resistant to antibiotics with recurrent treatment. To understand better the dynamics of the polymicrobial nature of the samples, the researchers looked for positive and negative associations among bacterial species. Along with other associations, they found that, in some participants, two bacterial species—*Escherichia coli* and *Enterococcus faecalis*—co-occurred on the catheter samples. Additional experiments confirmed this positive association, showing that *E. coli* can promote *E. faecalis* growth. Understanding the relationships among different bacterial species provides key insights for determining which species to target for antimicrobial treatment.

These findings suggest that the polymicrobial nature of catheter microbial communities along with development of antibiotic resistance could contribute to the risk of urinary tract infections in those using catheters long-term. Additional research is needed to characterize these interactions further, and the findings could lead to development of more effective prevention and treatment strategies for catheter-associated urinary tract infections.

Nye TM, Zou Z, Obernuefemann CLP,...Hultgren SJ. Microbial co-occurrences on catheters from long-term catheterized patients. Nat Commun 15: 61, 2024.

Insight Into Chronic Pain Experienced With Recurrent Urinary Tract Infections: Researchers have found that increased nerve growth and activation may be a major contributor to lasting pain and other symptoms experienced by people who frequently develop urinary tract infections (UTIs). UTIs, which are commonly caused by bacteria entering and then growing within the bladder, can cause symptoms such as frequent urination and pain in the lower abdomen or while urinating. People who develop two or more UTIs within 6 months or develop three or more within a year are diagnosed with recurrent UTIs (rUTIs), and women are especially susceptible to recurrence compared to men. People who experience rUTIs often continue to experience symptoms such as pain and increased urinary frequency even after the infection has cleared, a phenomenon that is not fully understood. Increased growth of nerve fibers through a process called nerve sprouting has been implicated as a contributor to some chronic pain conditions, and a hormone known as nerve growth factor (NGF) has previously been shown to be elevated in the urine of people who develop rUTIs.

Scientists have discovered pathways that may increase nerve growth and lead to pain that persists after recurrent urinary tract infections.

In a recent study, scientists investigated whether stimulation of nerve sprouting contributes to the persistent pain and symptoms associated with rUTIs. First, they obtained bladder biopsies and urine from women with rUTIs who did not currently have a bladder infection and from women with no history of rUTIs. They found evidence of more pain-sensing nerve activation among women with rUTIs than those without. To further study rUTIs in mice, the researchers injected *E. coli* bacteria directly into the bladders of female mice three times, with 7 days between each injection. Two weeks after the final infection, these "rUTI mice" displayed increased levels of pelvic sensitivity, urinary frequency, and nerve sprouting in their bladders compared with control mice. Significantly, the researchers observed that NGF was elevated in rUTI mice 7 days after the final infection compared with controls, suggesting that the molecule may be contributing to the increased symptoms observed in rUTI mice. Importantly, injecting uninfected mice with NGF for 7 days increased sensory nerve growth in a similar way, strengthening the hypothesis that the hormone contributes to increased pain in people with rUTI. Finally, the researchers discovered that a major source of NGF production in rUTI mice was a type of immune cell called a mast cell and that rUTI mice without such cells did not display pelvic pain sensitivity.

This study is an important step toward understanding the persistent pain symptoms sometimes associated with rUTIs. If confirmed, these findings suggest potential targets for symptom alleviation, such as NGF and mast cells, that could be pursued in future research.

Hayes BW, Choi HW, Rathore APS,...Abraham SN. Recurrent infections drive persistent bladder dysfunction and pain via sensory nerve sprouting and mast cell activity. Sci. Immunol 9: eadi5578, 2024.

DISCOVERING LINK BETWEEN HEMATOPOIETIC SYSTEM AND GESTATIONAL DIABETES

Uncovering a Biological Connection Between Gestational Diabetes and Long-Term Health of Offspring: Researchers have discovered that, in mice, the hematopoietic system (organs and tissues involved in blood production) plays an important role in linking gestational diabetes mellitus (GDM) to the later development of atherosclerosis in adult offspring. GDM, a form of diabetes that develops during pregnancy, is known to confer short- and long-term health risks to both mothers and offspring. Long-term effects include a greater risk of developing metabolic diseases (*e.g.*, type 2 diabetes, obesity) and atherosclerosis (plaque buildup that causes arteries to narrow, blocking blood flow). However, the underlying mechanisms by which GDM impacts risk of diseases across generations are unknown.

To address this gap, researchers generated two mouse models of GDM that mimicked human disease and studied their offspring. Experiments showed that GDM had long-lasting negative effects on the adult offspring's hematopoietic system. The offspring had hematopoietic features similar to those found in diabetic mouse models, even though they had no observable metabolic defects. The scientists also found that the adult offspring of the GDM mouse models had accelerated atherosclerosis development compared to the adult offspring of mice without GDM. Transplanting hematopoietic cells from GDM offspring into healthy mice caused increased atherosclerosis in the latter group, suggesting that the defects in the hematopoietic system contributed to the atherosclerosis development. Other experiments delved into defining the biological pathways linking GDM, the hematopoietic system, and atherosclerosis. The researchers found that the effects of GDM on atherosclerosis were dependent on proteins involved in increasing inflammation in the placenta. Preliminary analyses suggested that placental inflammation may be associated with epigenetic changes in the offspring's hematopoietic cells—such changes do not alter DNA sequences but can alter gene activity—although more research is needed to confirm this initial finding.

These results suggest that GDM in mice confers a "hematopoietic memory" across generations that is associated with atherosclerosis development in adult offspring. Because of the increasing prevalence of GDM, it is critically important to identify ways to protect the long-term health of offspring. If similar pathways are involved in people, these findings may one day offer clues about how to reduce or eliminate the harmful effects of GDM to protect the health of future generations.

Govindarajah V, Sakabe M, Good S,...Reynaud D. Gestational diabetes in mice induces hematopoietic memory that affects the long-term health of the offspring. J Clin Invest 134: e169730, 2024.

UNDERSTANDING HUMAN BLOOD CELL PRODUCTION

Unveiling Intricacies of Human Blood Cell Development: Researchers described a new technique that allows them to study hematopoietic stem cell (HSC) development into blood cells within people. HSCs are precursor cells that can produce different blood cell types, including red blood cells, platelets, and immune cells. Gaining a more detailed understanding of HSC differentiation into specific types of blood cells can provide insight into processes like aging and disease development and may even lead to future treatments. Past lineage tracing efforts—to "mark" and follow the progeny of individual HSCs as they develop into different blood cell types—would typically require the insertion of specific DNA sequences into cells through genetic manipulation. Though routinely used in animal models and in human cell lines in laboratories, this method can only be used in humans in very rare instances, thereby limiting understanding of blood cell development.

Researchers gained new knowledge about human blood with a new technique to follow mitochondrial DNA through blood cell development.

In this study, researchers relied on the sequence of DNA that is housed within mitochondria—essentially the biological power plants of the cell—referred to as mtDNA. Taking advantage of the fact that mtDNA is prone to sporadic mutations, they were able to use these mutations as naturally occurring markers to follow the lineage of different individual HSCs as their progeny cells developed into mature blood cells. When analyzing bone marrow cells (where HSCs are found) donated by healthy young individuals, the researchers were able to identify over 10 times more unique mtDNA mutations with their new method. Importantly, the

authors also identified similar types of mutations to those identified in previous studies, thereby validating their method. By tracking mtDNA mutations of single cells, the scientists developed maps of the relationships between HSCs and fully developed blood cells. They found that each group of HSCs identified went on to produce mature blood cells and that some showed preferences toward development into specific types of blood cells. The study researchers also observed that, in people over 70 years old, the fraction of cells with mtDNA mutations increased in comparison to younger individuals. However, HSCs of older participants also showed decreased diversity (number of unique mtDNA mutations), which has been associated with development of different cancers and blood disorders.

The findings from this study serve as a step toward more detailed insight into development of not only blood cells, but other cell types as well. Further study of the molecular processes behind development of mature cells from progenitor cells like HSCs may also provide insight into disease development and potential treatment or prevention strategies.

Weng C, Yu F, Yang D,...Sankaran VG. Deciphering cell states and genealogies of human haematopoiesis. Nature 627: 389–398, 2024.

Novel Regulator of Human Red Blood Cell Development Identified: Scientists demonstrated the role of a novel regulator known as "*GATA2AS*" in human blood cell development. Blood is composed of several different cell types—red blood cells, white blood cells, and platelets—that are produced from progenitor stem cells through a process called "hematopoiesis." This process is highly controlled to maintain the stem cells and to ensure that all blood cell types are produced properly. One way hematopoiesis is controlled is through the production of specific regulators at precise times in the maturation process. For example, as a cell moves toward becoming a red blood cell, production of a regulator known as GATA2 decreases and production of another regulator (GATA1) increases. Understanding how this process is controlled provides important insights into strategies to treat blood diseases and disorders.

Studies in mice previously revealed that "long noncoding RNAs"—a type of molecule encoded in DNA—could regulate the development of red blood cells. In humans, a long noncoding RNA known as "*GATA2AS*" is encoded within the *GATA2* DNA, but it was unknown whether *GATA2AS* played a role in human red blood cell development. Through genetic studies using human cells in the laboratory, the scientists showed that loss of *GATA2AS* resulted in changes to the genes activated in red blood cell development, such as a decrease in production of GATA2, and accelerated maturation of red blood cells. Additional experiments demonstrated that *GATA2AS* bound to thousands of locations in the genome and influenced the binding of proteins that activate genes, including many involved in hematopoiesis.

Collectively, these studies revealed *GATA2AS* as an important regulator of human red blood cell development. Additional research will provide further insights into the roles of *GATA2AS* and other long noncoding RNAs and could unlock potential new strategies to treat blood diseases and disorders.

Liu G, Kim J, Nguyen N, Zhou L, and Dean A. Long noncoding RNA GATA2AS *influences human erythropoiesis by transcription factor and chromatin landscape modulation. Blood 143: 2300-2313, 2024.*

Revealing a Tightrope Walk of Maternal–Fetal Immune Responses to Inflammation: Researchers found that, in mice, the maternal response to inflammation during pregnancy may inhibit immune responses in the fetus. Hematopoietic stem and progenitor cells (HSPCs) are special cells that can develop into all types of blood and immune cells. When exposed to inflammation caused by infection, disease, or other immune stimulants, HSPCs respond by adjusting the types and quantities of cells that they produce. For example, production of myeloid cells—blood cells that act as a first line of immune defense—is increased in response to inflammation. This response is called emergency myelopoiesis (EM), a process known to readily occur in adults. However, previous findings suggest that EM may not occur within developing fetuses, potentially leaving newborns highly susceptible to infections. This study sought to determine whether fetal HSPCs are able to activate the EM process in response to inflammation and to identify what, if anything, may hinder that process.

First, study researchers used cells from mice to compare the abilities of fetal and adult HSPCs to produce myeloid cells. They found that, while fetal HSPCs were more limited in this capacity than adult HSPCs, the fetal HSPCs were able to activate EM and increase myeloid cell production under some conditions. To determine whether fetal HSPCs in their natural setting were able to activate EM, the researchers injected pregnant mice with a bacterial immune stimulant to induce inflammation. They observed that HSPCs within the fetus were able to sense the inflammation (measured by an increase in

white blood cell production) but did not activate EM, suggesting that something may hinder this process. The researchers next assessed whether this could be due to a maternal immune factor produced during pregnancy to protect the fetus. Indeed, they identified a molecule known as IL-10 that promotes an anti-inflammatory environment during pregnancy and appeared to be responsible for the inhibition of EM from fetal HSPCs.

Poor fetal immune response to infections during late pregnancy contributes to higher risk of morbidity and mortality. Understanding why and how the fetal immune response is suppressed may reveal insights that could lead to new approaches to treat infections during pregnancy and in newborns. This study reveals a potential mechanism by which the maternal immune system can suppress the fetal EM process, highlighting a delicate balance of maternal–fetal immune responses during and after pregnancy. Further studies are needed to determine whether this is a consistent phenomenon across different types of infections or disease conditions; if this occurs in human maternal–fetal interactions; and whether this knowledge could potentially inform future therapies.

Collins A, Swann JW, Proven MA,...Passegué E. Maternal inflammation regulates fetal emergency myelopoiesis. Cell 187: 1402-1421, 2024.

FEATURE

Embedding Research in Clinical Care: Trial Aims to Improve the Lives of People With Multiple Chronic Illnesses

Managing chronic disease can be a difficult task, as it may involve taking the right drugs at the right time, implementing lifestyle changes, and making time to see doctors. For individuals with multiple chronic conditions, such as the "kidney-dysfunction triad"—a combination of chronic kidney disease (CKD), hypertension, and type 2 diabetes—disease management is even more challenging. These three diseases separately impact the kidney, heart, vasculature, and insulin sensitivity, but together they may further increase the risk for end stage kidney disease and premature death, demanding even more rigorous care and attention.

Clinicians strive to provide care that is based on high-quality, evidence-backed recommendations. However, the unique combination of three diseases can make it difficult to apply results from clinical trials that typically focus on one disease. To overcome this knowledge gap, NIDDK supported the Improving Chronic Disease Management with Pieces ("ICD-Pieces") Trial through the NIH Pragmatic Trials Collaboratory. Unlike a traditional clinical trial that separates the study from normal clinical care by creating study-specific protocols and services, the ICD-Pieces Trial sought to embed the study in already existing health care delivery systems. This design, called a "pragmatic clinical trial," allows for interventions to be analyzed in real-world clinical practice with a diverse patient population.

The ICD-Pieces Trial took place in Texas and Connecticut, enrolling over 11,000 male and female patients with kidney-dysfunction triad at 141 clinics to test whether a novel intervention could improve care for those living with these conditions. The trial split participants into two groups: The control group continued to receive the care they had already been receiving, while the intervention group had a new technology available to their clinical team aimed at coordinating care. This technology utilized electronic health records and practice facilitators (specially trained nurses and pharmacists) to assist patients with coordinating care between primary care physicians and disease specialists and creating individual care goals. It also helped clinicians improve data collection, recommend evidence-based interventions for each patient, and identify complications at an early stage.

The researchers hypothesized that the increased coordination in care would result in fewer visits to the hospital for patients, as identifying and addressing complications sooner should lead to less adverse medical events. However, after a year of follow-up, there was no difference in the rate of hospitalization between the intervention and control groups. Additionally, they did not find differences in secondary outcomes, including cardiovascular events like heart attacks and strokes, the need for dialysis, or death. Some factors—such as the relatively short follow up time of 1 year, differences in adherence to treatment, and the timing of the intervention in the disease course—may have limited the efficacy of the treatment, and these caveats could be explored further. However, at this point, the research does not support the idea that utilizing this particular approach improves outcomes in the patient population with kidney-dysfunction triad.

While the study data did not support the hypothesis, ICD-Pieces nevertheless made key contributions to research. For example, the study helped to further researchers' understanding of how to design and implement pragmatic clinical trials, providing lessons that will be carried forward into new studies to test interventions in patients with multiple chronic conditions. Additionally, knowing what interventions do not work in different patient populations helps to inform clinical care guidelines. Future NIDDK-funded clinical trials will improve health in people living with multiple complex chronic diseases by building on the foundation laid by ICD-Pieces.

Vazquez MA, Oliver G, Amarasingham R,...Toto RD; for the ICD-Pieces Study Group. Pragmatic trial of hospitalization rate in chronic kidney disease. N Engl J Med 390: 1196-1206, 2024.

FEATURE

Workshop on Preparing for Kidney Precision Medicine Clinical Trials

Over 300 participants, including people with kidney disease, their families, scientists, and representatives from federal, regulatory, and pharmaceutical sectors, joined in a 2-day meeting in March on the future of kidney precision medicine trials. While celebrating recent advances in basic, translational, and clinical research, the assembled community acknowledged the need for more precise, effective, and safe therapies to bring the right treatment to the right patient at the right time.

Participants with kidney disease and their family members shared insights into their lived experiences and the failings of current treatment approaches. Advocates for people with kidney disease presented data about the desire for new therapies and the patient community's interests in helping shape the research agenda and in participating in clinical trials to improve kidney health.

Investigators shared results of research that is now distinguishing between similar-seeming conditions that contribute to the national burden of chronic and acute kidney diseases and shedding light on why these conditions respond to treatment in differing ways. Participants presented research findings on chronic kidney disease and acute kidney injury, including information generated from the Kidney Precision Medicine Project. New insights on polycystic kidney disease, glomerular diseases, and vascular access were also discussed. These discoveries not only underline the need, but also help define the scope of future precision clinical trials.

Testing new therapies efficiently and effectively will require biomarkers with relevance to the specific disease mechanisms that have come into focus through research. Biomarkers identified from prospective observational study data, established biobanks, and data and biospecimens generated in clinical trials may help match would-be participants with appropriate clinical trials and could also help monitor treatment response during such studies. Scientists who specialize in developing and/or validating assays for use in human investigations are therefore key members of precision clinical trial teams.

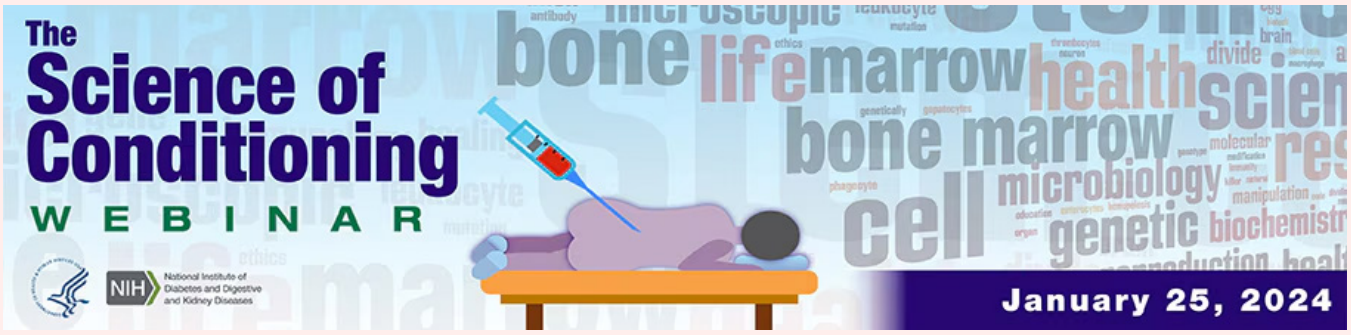
To help participants envision what kidney precision medicine trial platforms might look like, the workshop also featured an overview of ongoing precision medicine programs in cancer therapeutics. Reviewing these consortia yielded insight into effective

organizational structures for precision trial programs and ways to initiate them. The presentations also highlighted the value brought to specific populations and therapeutic areas when teams are assembled with a common goal to advance patient health.

Speakers emphasized that teams advancing the field of kidney precision therapeutic development will benefit from diverse expertise for both repurposing existing drugs and devices as well as developing novel ones. The work will require expertise in clinical trial design, mechanism discovery, pharmacogenetics, pharmacokinetics, bioinformatics, biostatistics, and regulatory processes; patient and clinician perspectives; and input from representatives of the biotech/pharmaceutical industry. Perhaps most important of all will be the perspectives and lived experiences of those living with these diseases, as well as the people who care for them: Any future NIDDK-supported kidney precision medicine trial will be informed by their voices.

FEATURE

Workshop Held to Stimulate Research on Stem Cell Transplant-Based Treatment of Non-Cancerous Blood Disorders



On January 25, 2024, NIDDK hosted a workshop entitled "The Science of Conditioning" where participants shared recent insights on the effects of stem cell transplantation–based treatment regimens on health outcomes of people with noncancerous blood disorders such as sickle cell disease and different types of anemias. This meeting provided a platform for dynamic discussions with the goals of establishing productive collaborations and stimulating new ideas towards improving the treatment of individuals living with hematological diseases.

Hematopoietic stem cell transplantation (HSCT) can serve as a curative therapy for people with various types of blood disorders by enabling their bodies to generate healthy blood cells that they cannot naturally produce. The medical steps taken to prepare a person's body for HSCT are referred to as a conditioning regimen. These regimens include approaches such as chemotherapy, immunotherapy, and radiation, which typically indiscriminately wipe out most of the resident cells in the bone marrow to make room for new cells to be transplanted and produce healthy blood cells.

These broad approaches can be harsh on a person's body, so treatment of noncancerous blood diseases requires balancing between the broadly acting, potentially toxic effects of classic conditioning and the potential of transplant rejection or failure in the absence of adequate conditioning. Recent outcomes of clinical trials have highlighted the critical need to understand the impact of conditioning therapy in these hematological disorders and explore alternative regimens.

The workshop highlighted emerging discoveries related to innovative conditioning regimens as well as identified knowledge gaps to inform future research. Participants discussed topics like investigation of the bone marrow environmental niche to better understand the dynamics of cells residing there; exploration of less harsh, more targeted approaches to cell depletion; and

development of methods to enhance characteristics of transplanted stem cells. Breakout discussions facilitated by NIDDK program officials encouraged participants to brainstorm questions in the field, including how to improve current technologies to measure success of transplant outcomes and which model systems best reflect human disease when addressing key questions about conditioning.

Overall, the workshop carved a path for generation of new hypotheses and collaborations and took a step toward improving the experience and outcomes of HSCT treatment among people with noncancerous blood disorders.

A more detailed summary of the meeting is available to the public *here* on the NIDDK website.

Bob: PUSHing Forward to Prevent Recurrent Kidney Stones

Bob participated in the PUSH clinical trial, which tested whether behavioral strategies to increase water intake could prevent kidney stone recurrence

Bob, a 70-year-old retiree from the Midwest, was first diagnosed with kidney stones (also known as urinary stone disease) about 25 years ago. At the time, he recalls feeling "immediate pain and nausea to the point where I was completely bent over." He promptly went to the emergency room and was told that he had kidney stones—pebble-like material that forms in the kidneys when high levels of certain minerals are in the urine. His kidney stones were small enough that he would only need fluids to resolve them. "The next day or so was not always comfortable, but they did pass on their own," he remembers.

Bob's doctors encouraged him to drink more fluids, citing mild dehydration as a cause of his kidney stones, especially because he was very physically active and thus susceptible to dehydration. Along with training for a marathon for his 50th birthday, "I was always active in judo or TaeKwon-Do, or just working out at the Y," he says. Since his first kidney stone, Bob has had recurrences every 7 to 10 years. "It hasn't been a constant thing, but … when you have an issue, it is immediate and painful," he says.

Speaking on the importance of participating in the PUSH clinical trial, Bob says, "When I was given the opportunity to be a part of this program, I said, absolutely, I want to be a part of that," as he knew the findings could help others like him living with recurrent kidney stones.

PARTICIPATING IN CLINICAL TRIALS: A FAMILY TRADITION

When his doctor retired, Bob had to search for a new one, which is how he connected with Washington University in St. Louis (Wash U). He was assigned to Dr. Alana Desai, a urologic surgeon who has expertise in the medical and surgical treatment of kidney stones. In 2021, while Dr. Desai's office was working with Bob to manage a kidney stone recurrence, they mentioned that they were a participating site in a clinical trial called the Prevention of Urinary Stones with Hydration, or PUSH. Because inadequate hydration is a main risk factor for kidney stone development and recurrence, PUSH was testing whether behavioral strategies to increase water intake could prevent kidney stone recurrence. "When I was given the opportunity to be a part of this program, I said, absolutely, I want to be a part of that," he recalls.

PERSONAL PERSPECTIVE

Bob cites his mother as his inspiration for joining the trial. After she was diagnosed with terminal cancer, he says that "she was offered the option to join a research program.... And she said, 'even though my time on Earth is limited, if I can do anything to help somebody else, I want to be a part of that.'" Her example made it an easy decision for him to enroll in PUSH, as he knew that findings could help others like him living with recurrent kidney stones.

ENROLLING IN THE PUSH TRIAL

Bob was randomly assigned to the intervention arm of the PUSH trial. Participants in both the intervention and usual care (control) arms received digital "smart" water bottles that connect via app to a phone to help track water intake. In addition to the water bottles, Bob and others in the intervention arm also got fluid intake prescriptions, which indicated the additional amount of water they needed to consume daily from the bottle, earned financial incentives for meeting daily water goals, and participated in coaching and structured problem-solving sessions. (More information on the PUSH trial is found in the box at the end of this perspective.)

Bob speaks highly of the research team. "Half of working with the medical team is, are they willing to listen and be as interested in my answers as they are in their questions?" he explains, adding that the team asked great follow-up questions to ensure they understood his experience exactly.

When Bob first enrolled in PUSH, he began tracking his water intake with the smart water bottle that connected to an app so that the researchers could track how he was doing with his intake. The app "would shoot off little fireworks when I reached my goal, but it also yelled at me if I drank more than twice my goal," he says with a laugh. The study allowed him to drink whatever he wanted, but only water counted toward his daily goal.

It took Bob a few months to adjust to the study protocol fully, but he found the water bottle to be extremely helpful in increasing his water intake. He always carried it with him, taking it to meetings and even fishing. Over time, he started reducing the amount of non-water beverages he was drinking. He reflects, "I did really cut back on the amount of carbonated soda I was drinking and discovered that, except on special occasions, I didn't want that, because I really enjoyed just drinking water or water with lemon." Beyond his adjustment period, Bob emphasizes that the study "became a part of my daily life." He states that he did not find the monetary incentives or coaching session strategies to be motivating for him personally—he nearly always met his water intake goals using only the smart water bottle.

Every 6 months, Bob visited his study site at Wash U and filled out questionnaires about his experiences, reporting on side effects and other information relevant to the trial. He speaks highly of his study team, offering praise for their bedside manner, their approach, and their ability to listen. For Bob, having a research team that can ask good questions and be attentive to his responses was a key part of the experience: "Half of working with the medical team is, are they willing to listen and be as interested in my answers as they are in their questions?" He adds that the team asked great follow-up questions to ensure they understood his experience exactly.

AN OPTIMISTIC FUTURE

Since joining the PUSH trial, Bob has not had a recurrence of kidney stones. He remarks that the benefits of being hydrated seemed to extend beyond even that: "I just felt great during the program.... I know it helped my kidney function, but my whole body responded so much better when I stayed hydrated." Also, importantly, even since concluding his formal participation in PUSH in January 2024, Bob still carries

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his smart water bottle with him and maintains his fluid intake—demonstrating that the strategies he learned in PUSH to increase his water intake are feasible for him to continue beyond the trial. He notes that he does not always track as diligently as he did while in the trial, but he estimates reaching his minimum fluid goal an impressive 90 percent of the time, if not more. Regarding his prospects of having another kidney stone, Bob says, "I'm still cautiously optimistic that this will be a solution for that, and that was one of the things that Dr. Desai said—that our goal is that I would never have another kidney stone again."

"I just felt great during the program…. I know it helped my kidney function, but my whole body responded so much better when I stayed hydrated," Bob says, describing how increasing water intake as part of the PUSH trial benefitted his health.

Bob recently entered his second retirement. His first career was in accounting and business management, and he has spent the last 40 years serving as a local church pastor and working with nonprofits. After his initial retirement, he made a brief but meaningful return to work, helping churches navigate through transitions, such as examining their work in the community to address food insecurity. Much of his time is now spent pursuing his hobbies as an avid fly fisherman and an amateur astronomer, as well as taking his 7-year-old English cream golden retriever to hospitals, nursing homes, schools, and libraries to provide comfort as a therapy dog.

Having another kidney stone is not on Bob's retirement to-do list. The behavioral strategies he learned in PUSH can allow him to continue to meet his water intake goals and reduce his future risk of a stone recurrence. Importantly, his decision to follow in his mother's footsteps and participate in clinical research is adding critical knowledge about the prevention of recurrent kidney stones in others.

More Information on the Prevention of Urinary Stones with Hydration (PUSH) Clinical Trial

Kidney stones (also known as urinary stone disease) are a common ailment in the United States and can be very painful. They form in the kidneys when solid deposits develop due to a high concentration of certain minerals during the production of urine. Persons who have had a kidney stone are more likely to develop another. One of the main risk factors for development and recurrence of kidney stones is inadequate hydration, which can lead to low daily urine volumes and thus higher salt and mineral concentrations. Evidence suggests that significantly increasing fluid consumption can prevent or delay recurrence of kidney stones. Although people who have had kidney stones are commonly counseled to increase their fluid intake, this can be challenging for many reasons, ranging from simple forgetfulness to limited bathroom access.

In light of these challenges, NIDDK's Urinary Stone Disease Research Network—a network of investigators designing and conducting research in adults and children with kidney stones—developed and launched the Prevention of Urinary Stones with Hydration, or PUSH, randomized clinical trial. PUSH is testing the effectiveness of a multi-component behavioral intervention strategy to increase water intake and consequent urine output on preventing

PERSONAL PERSPECTIVE

kidney stone recurrence in adolescents and adults. The trial enrolled 1,658 volunteers aged 12 and older with a history of stones, with daily urine output lower than the study target, and who owned a smartphone or tablet.

PUSH participants were randomly assigned into a usual care (control) group or an intervention group for a 2-year follow-up period. In both groups, participants were given a commercially available "smart" water bottle that tracks water consumption via an app. Participants in the usual care group received standard recommendations to increase their overall fluid intake and urine output according to medical professional society guidelines. They were allowed but not required to use the smart water bottle, and they received monetary compensation for completion of study activities.

The intervention group received usual care information and were also engaged in a behavioral change program. This program included a fluid intake prescription indicating the additional amount of water they needed to consume daily via the smart water bottle to achieve their target urine output; financial incentives (which gradually tapered to zero) for meeting daily water goals; coaching and structured problem-solving sessions in year 1 to help overcome individual barriers to meeting fluid intake goals; and access to "low-touch" interventions (*e.g.*, text or telephone reminders) in year 2.

Participants in both the intervention and usual care groups performed periodic 24-hour urine collections at home, had kidney imaging performed at the beginning and end of the trial, and filled out online questionnaires about their general health and stone disease every 3 months; adult participants also filled out questionnaires about urinary symptoms every 6 months.

While the trial is over, PUSH researchers are now comparing data from the two groups regarding the number and timing of symptomatic stone events as defined by the study. This will enable them to determine whether the structured, phased, behavioral change intervention provides a significant benefit over usual care through secondary prevention or delayed recurrence of stones that induce symptoms and/or require medical intervention.

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