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As described in this chapter, researchers have found that in mice, kidney damage caused by polycystic kidney disease (PKD) can largely be reversed by turning on the normal version of a gene that was initially faulty. PKD is a form of chronic kidney disease that reduces kidney function and may lead to kidney failure. PKD causes many fluid-filled cysts to grow in the kidneys; unlike the usually harmless simple kidney cysts that can form in the kidneys later in life, PKD cysts can change the shape of the kidneys, including making them much larger. The most common form of PKD is autosomal dominant polycystic kidney disease (ADPKD), which results from mutations in the human \textit{PKD1} or \textit{PKD2} gene. In a new study, scientists induced PKD in mice by inactivating either of the corresponding mouse genes—\textit{Pkd1} or \textit{Pkd2}—specifically in the kidney. As illustrated in the image, mice with inactivated \textit{Pkd1} developed enlarged kidneys containing the characteristic cysts that worsened over time, here shown at 13 weeks (B) and 16 weeks of age (C); these results were in stark contrast to non-cystic kidneys from mice with the normal \textit{Pkd1} gene (A). However, when the researchers later used a genetic technique to reactivate the \textit{Pkd1} gene, the cysts resolved, and the kidney damage was largely reversed (D). These findings may lay the foundation for developing gene therapy approaches to treat people with ADPKD.

\textit{Image provided by Dr. Stefan Somlo, Yale University. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Genetics, Renal plasticity revealed through reversal of polycystic kidney disease in mice, Dong K, Zhang C, Tian X, Coman D, Hyder F, Ma M, and Somlo S. Copyright © 2021.}
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 37 million American adults have impaired kidney function—also called chronic kidney disease (CKD).\(^1\) CKD has two main causes: high blood pressure and diabetes. The increases in obesity and type 2 diabetes in the United States in recent years—especially among children and adolescents—have grave implications for the Nation’s health, as young people with these conditions are likely to face serious health complications at an earlier age than people who historically have developed these conditions later in life. CKD can also result from other factors, as noted below.

In 2019, over 809,000 Americans were living with end-stage renal (kidney) disease.\(^2\)

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

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.

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. 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. 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.

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, 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. 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. 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.

Research on UCPPS is one example of how 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. Thus, 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, NIDDK is supporting research to better understand factors that contribute to bladder health over the lifespan, with the ultimate goal of preventing LUTS.

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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.

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

ADVANCING KNOWLEDGE OF KIDNEY PHYSIOLOGY

Detailed “Kidney Atlas” Characterizes Cells of the Healthy Adult Kidney: In an advance that is dramatically deepening our understanding of normal kidney physiology, researchers have produced a reference source that shows in detail the way healthy adult human kidneys are organized at the cellular level. The kidney is a remarkable example of biological architecture, with a complex array of structures called nephrons, each consisting of many cell types. Together, these structures perform the critical job of regulating fluid and salt levels in the body, among other tasks. Subtle disruptions of kidney cell function can therefore lead to serious health consequences.

The NIDDK-led Kidney Precision Medicine Project (KPMP) seeks to revolutionize kidney care by identifying critical cells, pathways, and targets for potential novel kidney disease therapies and prevention strategies. To achieve this lofty goal, KPMP investigators first developed an intricate “atlas” of the healthy human kidney for comparison purposes. They accomplished this through a comprehensive analysis of kidney tissue biopsies ethically obtained from study volunteers. This atlas delineates the biology of individual cells in various parts of the nephron and its surrounding tissue, demonstrating how they are defined not only by their position in the kidney, but also by the precise molecular signatures of genes and proteins active within them. Through their analyses, the researchers also found areas within the nephron that might be vulnerable to damage resulting from low oxygen levels, and enhanced understanding of other aspects of kidney function.

The Kidney Precision Medicine Project has produced an “atlas” revealing remarkable cellular and molecular details of the healthy human kidney.

The KPMP research team has made their kidney atlas available on the web to share this valuable new resource broadly with the research community. Thanks to these discoveries, KPMP scientists and other researchers are now poised to compare biopsies from diseased kidneys against this reference atlas to yield critical new insights into the causes of kidney diseases and new ways to prevent, diagnose, and treat them.


RESEARCH ON KIDNEY DISEASE

Studies Identify Immune Cell Types Associated with Progression of Different Forms of Kidney Disease: A recent study of chronic kidney disease (CKD) in mice shows that one type of immune cell may have an important role in accelerating kidney fibrosis, or scarring, which can lead to kidney failure, while another study linked a group of immune cell types to accelerated cyst growth after kidney injury in a mouse model of cystic kidney disease.

The immune system is thought to drive inflammation leading to kidney fibrosis and loss of function in common forms of CKD, but the mechanisms by which it does so have not been well understood. A group of researchers therefore examined kidney cells of male mice with CKD that were showing signs of inflammation and fibrosis and discovered the cells were secreting a factor that attracts a type of immune cell known as a basophil.
In further experiments, they found that they could slow the process of fibrosis by reducing the number of basophils in the animals or interfering with the basophils’ ability to signal to other cells. Notably, an analysis of kidney cells from people with and without CKD showed that CKD was associated with substantially higher basophil levels and that higher basophil levels correlated with more fibrosis. These results suggest that basophils may play an important role in the progression of common forms of kidney disease, and that it may one day be possible to slow CKD progression by interfering with basophils.

Another group of researchers sought to investigate the role of various immune cells in the progression of cystic kidney diseases like autosomal dominant polycystic kidney disease (ADPKD). Previous research had suggested that kidney inflammation caused by injury or infection results in rapid acceleration of the disease by promoting both the formation and growth rate of cysts. The researchers therefore examined female mice with a model of cystic kidney disease and found several differences in the proportion of different types of immune cells between healthy kidneys, kidneys with slow-growing cysts, and kidneys where cysts grew rapidly due to injury. In particular, there were differences in a group of immune cells associated with adaptive immunity (i.e., cells that acquire the ability to fight an infection from previous exposure to the same pathogen). To explore the roles of these cells in kidney cyst growth, they used a technique to eliminate adaptive immune cells from the mice. Interestingly, kidney injury did not lead to the usual acceleration of cystic disease in mice without the adaptive immune cells, while the absence of these cells did not affect disease progression in uninjured kidneys. If these cells are found to have similar effects on human kidney cysts, it may one day be possible to protect people with ADPKD or other cystic kidney diseases from rapid disease progression after injury or infection by modulating the activities of specific groups of immune cells.


Metabolites Linked to a Range of Symptoms Experienced by People with Chronic Kidney Disease: Researchers have identified metabolites (molecular byproducts of metabolism) that are associated with specific symptoms of uremia—a condition in which poor blood filtration from reduced kidney function leads to a buildup of toxins in the blood—a discovery that could one day lead to improved care for people with chronic kidney disease (CKD). People with CKD often experience a range of uremic symptoms that adversely affect quality of life. These symptoms can be gastrointestinal (e.g., loss of appetite, nausea, vomiting) or neurological (e.g., reduced alertness, forgetfulness, lack of energy) in nature. While blood toxins are known to contribute to uremic symptoms, the specific causative metabolites are unknown. In a recent study, scientists determined the blood levels of more than 1,100 metabolites in 695 participants with CKD (38 percent female, 86 percent White) and developed a “score” for each uremic symptom based on reported severity and duration in each individual. They then looked for associations between metabolite levels and symptom scores. Eleven metabolites were found to be associated with gastrointestinal symptoms and seven metabolites were associated with neurological symptoms. The authors acknowledge that the size of the cohort was relatively small, and the relative representation of CKD causes within the cohort may limit the applicability of the findings. Laboratory testing, validation, and randomized controlled trials would be needed to determine definitively whether specific metabolites cause certain uremic symptoms. Further studies of the metabolites identified in this study could lead to novel therapeutic approaches to alleviate the uremic symptoms experienced by many people with CKD.


Reversing Polycystic Kidney Disease in Mice: Using mouse models, researchers showed that, in early stages of polycystic kidney disease (PKD), kidney damage can be reversed by reactivating an inactive gene—findings that raise the possibility of using gene therapy to treat people with PKD. PKD is a genetic disorder that causes numerous fluid-filled cysts to grow 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 most common form of PKD is autosomal dominant polycystic kidney disease (ADPKD), which results from mutations...
in either the PKD1 or PKD2 genes. Previous research has shown that therapies targeting molecular pathways affected by disruption of the PKD1 or PKD2 genes can slow progression of the disease, but not reverse the kidney damage.

In a new study, scientists used complex genetic strategies to first inactivate either of the corresponding genes in mice—Pkd1 or Pkd2—specifically in the kidney, which led to enlarged kidneys, characteristic cyst formation, and other forms of damage. They later reactivated the genes relatively early in the course of the disease, which led to a dramatic reduction in kidney size in the mice. Further analyses showed that the gene reactivations reversed many hallmarks of PKD: the cysts resolved, cell and tissue structures returned to normal, and many signs of kidney damage (e.g., inflammation, tissue scarring) dramatically improved. When the scientists waited to reactivate the genes until the mice had reached an advanced stage of PKD, they observed partial, but not complete, reversal of disease characteristics, suggesting that eventually some damage from the disease can become permanent. Although kidney damage was once considered almost invariably permanent, this study demonstrates that, in some cases, reversal may be possible, at least in mice. If these findings hold true in humans, gene therapy approaches may one day be able not just to slow disease progression in people with ADPKD, but potentially to reverse it.


**In mice, kidney damage caused by autosomal dominant polycystic kidney disease was largely reversed by activating the normal version of a faulty gene.**

Chronic Kidney Disease in Children Affects Brain Development: Researchers have observed differences in brain structure in children with chronic kidney disease (CKD) compared to children without CKD. CKD is characterized by a reduced ability of kidneys to filter blood the way that they should over an extended period of time. Diabetes and high blood pressure are the leading causes of CKD in adults. However, the most common causes of CKD in children are kidney birth defects or genetic diseases. Deficits in mental function are often associated with CKD in pediatric patients, with children displaying difficulties concentrating, learning, and remembering. While these cognitive deficits are known to manifest, there have been very few brain-imaging studies to determine their cause.

In this study, researchers used a brain imaging technology called diffusion weighted magnetic resonance imaging to view the integrity of tissues deep in the brain known as white matter. The researchers compared brain scans of 17 boys with CKD (ages 6 to 16) to 20 healthy boys (ages 7 to 16). Their aim was to identify differences between the groups and to discern their potential links to cognitive deficits in those with CKD. The analysis revealed reduced white matter integrity in children with CKD that mapped to multiple distinct brain regions when compared to children without CKD. The scientists did not, however, find that the observed decrease in white brain matter integrity correlated with cognitive deficits. In fact, the researchers observed that, among the children with CKD, there was an unexpected potential association between higher white brain matter integrity and decreased executive functions (mental processes directing a child's thought, action, and emotion during problem solving).

This study suggests that there are differences in the brains of children with CKD compared to children without the disease. Further research on a larger number of children, including girls as well as boys, may provide insight into whether white matter differences contribute to the cognitive deficits observed in children living with CKD and whether the correlations observed in this study are truly representative of the population.


**PREVENTING KIDNEY STONE RECURRENCE**

Removing Asymptomatic Kidney Stones During Symptomatic Stone Removal Surgery May Result in Lower Risk of Recurrence: A small study has found that people have a lower chance of future kidney stone problems if smaller, asymptomatic kidney stones are also removed during surgery to remove larger, symptomatic ones. Kidney stones are hard, pebble-like structures that form in the kidneys when a person has high levels of certain minerals in their urine. Depending on their location and size, some kidney stones may be able to pass through the urinary tract without treatment. Others, however, can cause complications including severe pain, bloody urine, and urinary tract infections. Asymptomatic kidney stones are more common than...
and are often found alongside of symptomatic stones. There are conflicting views about the impact of leaving these asymptomatic stones behind during removal of symptomatic ones, and current guidelines leave it to doctors and patients to decide whether to remove them or simply monitor for recurrence of symptoms.

Researchers found that removing both symptomatic and asymptomatic kidney stones during the same surgery may reduce the likelihood of recurrence.

One approach to treatment for people with symptomatic kidney stones is endoscopic surgery, during which a small, thin camera is inserted into the urethra to find and remove any stones. In a recent study, 73 people undergoing endoscopic surgery for removal of symptomatic kidney stones were randomized either to have their asymptomatic stones removed during the procedure (treatment group) or not (control group). Both groups were then monitored up to 5 years post-surgery for recurrence in the form of an emergency room visit for stones on the same side as the removal, subsequent stone removal surgery on the same side, or visualized growth of an asymptomatic stone via a CT scan. The researchers found that recurrence occurred substantially more often in the control group than in the treatment group—63 percent compared to 16 percent—and that the time to recurrence was an average of 697 days longer in the treatment group than in the control group. Removal of asymptomatic stones did increase the duration of the surgery time, usually by less than 30 minutes.

The findings from this study suggest that removing both symptomatic and asymptomatic kidney stones during endoscopic surgery may reduce the likelihood of recurrence of stone-related complications. It is important to note that this was a small study in which approximately 90 percent of participants were White, so it is not yet clear whether the results will apply broadly across the population. However, if these findings are replicated in larger, more diverse studies, they could lead to new recommendations that may help reduce the risk of kidney stone recurrence.


IDENTIFYING NEW THERAPEUTIC TARGETS FOR BENIGN PROSTATIC HYPERPLASIA

Potential New Therapeutic Targets To Treat Benign Prostatic Hyperplasia: Two recent studies explored new potential approaches for treating prostate enlargement. The prostate, a small gland surrounding the urethra just below the bladder, is part of the male reproductive system and commonly becomes enlarged with age. This condition, called benign prostatic hyperplasia (BPH), is caused by the non-cancerous growth of the prostate due to increased reproduction of cells. As the prostate enlarges, it may squeeze the urethra and affect the flow of the urinary stream leading to symptoms involving changes or problems with urination. Many available BPH therapeutics aim to relax the muscles of the bladder and prostate to allow for urine flow.

Scientists studied new approaches to lessen the symptoms of benign prostatic hyperplasia, which could pave the way for needed alternative therapies for this condition.

One study utilized mouse models to explore the impact of targeting a protein called soluble guanylate cyclase, or sGC, on BPH symptoms. This protein is involved in proper functioning (contraction and relaxation) of muscles in the bladder and prostate and affects other processes, such as cell proliferation. Although some approved medicines treat BPH by affecting other proteins in the same pathway, they occasionally lose their effectiveness. In this study, researchers compared urination and prostate characteristics of aged mice displaying BPH-like symptoms with those of younger adult mice. Treatment of aged mice with an sGC-activating compound called cinaciguat for 2 weeks was able to restore normal urinary function in the BPH mice. The researchers also found that cinaciguat was able to reduce the frequency of bladder contractions in a different mouse model of BPH that mimics resistance to some approved therapeutics.

Another study investigated the contribution of autoimmune inflammatory diseases to BPH and the use of autoimmune disease therapeutics to treat the condition. Researchers analyzed the medical records of 112,152 men over the age of 40 and found the prevalence of BPH was substantially higher among individuals with autoimmune diseases compared to...
those without. However, in further analysis of each BPH diagnosis in relation to the timing of an autoimmune disease diagnosis, the researchers found that BPH was less common in males previously diagnosed with an autoimmune disease compared to those who were not. This result suggested that prior autoimmune disease-specific treatments may effectively treat or reduce the development of BPH. The researchers observed that tissue from donated human BPH prostates contained high levels of an inflammatory molecule, tumor necrosis factor (TNF), and found that TNF exposure triggered certain cells from human prostates to multiply. The researchers therefore investigated whether a class of anti-inflammatory autoimmune disease therapeutics known as TNF antagonists might be effective for treating BPH. Indeed, analyses of prostate tissue donated from people with BPH and of two different BPH mouse models revealed that a TNF antagonist reduced cell multiplication and markers of prostate inflammation compared to untreated controls.

Because TNF antagonist treatment can result in serious side effects, future studies to identify safer alternatives to reduce the inflammatory aspects of BPH will be important. If new treatments, including anti-inflammatory medications or cinaciguat or another sGC activator, are shown to be safe and effective, individuals with BPH may one day have valuable alternatives to existing therapies.


**INVESTIGATING WAYS TO PREVENT BLOOD DISORDERS**

Ferreting Out a Possible Way To Inhibit Ferritin Processing and Prevent Iron Overload: Research in mice suggests it may one day be possible to treat hemochromatosis by inhibiting a protein that can contribute to the overabsorption of iron. The body responds to iron deficiency by absorbing iron through the small intestine. The intestinal cells protect themselves from potentially toxic iron levels by packaging the absorbed iron into a protein complex called ferritin. As needed, the cells process the ferritin and release iron into the bloodstream. The body responds to sufficient iron levels by inhibiting this process to help avoid a potentially toxic iron glut. Unfortunately, this inhibitory system sometimes goes awry, allowing the body to absorb and release too much iron, a dangerous condition known as hemochromatosis.

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Research has now illuminated new details on the process of ferritin processing, revealing a potentially beneficial approach to treating hemochromatosis. Scientists identified a protein known as NCOA4 that plays a key role in processing ferritin to allow release of iron in the blood. In mice with a version of hemochromatosis, eliminating the protein from intestinal cells protected the animals from iron overload, while still allowing sufficient iron absorption to meet their needs. If the process is found to work the same way in people, and if a safe and effective way to control NCOA4 in the intestine can be identified, it may one day provide an effective means for treating hemochromatosis to people with the disease.

NIDDK hosted a virtual, 2-day workshop to catalyze efforts toward overcoming structural racism and achieving health equity in kidney disease. Structural racism is the embedded social, political, and economic system in which policies, practices, and institutions systematically create inequalities in resources and opportunity, thereby creating and perpetuating the marginalization of communities. Structural racism permeates society, impacting sectors such as housing, education, employment, and health care. The existence of structural racism has led to adverse social determinants of health, such as housing inequality, food insecurity, health care inequities, and other damaging factors that impact quality of life.

Health disparities are the preventable differences in the burden of disease experienced by people of racial, ethnic, and other minorities. Many social determinants of health—such as restricted access to health-promoting resources or marked differences in cost or quality of treatment—contribute to health disparities.

Kidney disease is one example of a disease with substantial disparities in health care and health outcomes. Kidney disease spans a broad array of diseases and conditions that affect millions of Americans and poses a significant public health issue. People who belong to racial and ethnic minority groups experience reduced access to and quality of nephrology referrals, home dialysis modalities, and kidney transplants, and they are at higher risk for kidney disease and failure.

Health equity (i.e., the ability for each individual to achieve his or her full health potential) cannot be achieved without addressing the mechanisms by which structural racism leads to disparities. NIDDK recognizes its responsibility to seek out opportunities to address both the upstream (e.g., systemic policies) and downstream (e.g., direct care differences) causes of racial and ethnic disparities in kidney disease. The NIDDK workshop “Designing Interventions That Address Structural Racism to Reduce Kidney Health Disparities” held February 24-25, 2022, sought to address two key goals: to describe the mechanisms through which structural racism contributes to health and health care disparities, and to identify actionable research recommendations for interventional research.

In keeping with NIDDK’s commitment to engaging diverse stakeholders, participants in this workshop included kidney disease and health disparities experts; people with kidney disease, as well as their families and caretakers; and other key stakeholders—all of whom brought a wide array of experience and expertise.

Issue experts reviewed the many ways that structural racism underlies health care systems and practices and the ways it is reflected in health disparities, particularly for people with kidney disease. People with kidney disease and their caregivers spoke to their lived experiences, identifying gaps in care and opportunities for improvement.

Through robust discussions, participants considered numerous prospects for intervention, including: mitigating individual burden by seeking broad structural changes; promoting patient-centered outcomes through community engagement; applying
an anti-racist lens to research; adopting health care models and practices—such as increased insurance access, improved data collection, broadened types of care, and reinforcement of safety nets—that advance health equity; encouraging long-term financial investments in research and increased access to research funding; increasing scientific workforce diversity; and building organizational capacity to advocate for change. In doing so, participants laid the framework for NIDDK-funded initiatives focused on dismantling or addressing the effects of structural racism to reduce disparities in care and improve outcomes for people living with kidney disease.

A summary of the meeting is available to the public here on the NIDDK website.
Meeting Held To Discuss Research on the Relationship Between Enlarged Prostate and Lower Urinary Tract Symptoms

On March 30 and April 1, 2022, NIDDK hosted a virtual workshop entitled "BPH and Male LUTS: Intersection between Pathology and Disease." The workshop sought to integrate recent understandings on the origins of, and symptoms associated with, prostate enlargement. The overall goals were to better understand the condition, assess the effectiveness of current treatments, and potentially determine new directions for improved therapies.

Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland that affects 50 percent of men over age 50 and 90 percent of men over age 80. Those with BPH often experience lower urinary tract symptoms (LUTS), which include difficulty with emptying the bladder, an urgency to urinate, and/or increased urination frequency.

Men who experience LUTS are typically first treated with medications that reduce the size of the prostate and relax the muscles of the bladder and prostate. Additionally, treatment can include resection (surgical removal) of the prostate. These treatments are not always successful in managing LUTS, however, and research has shown that the size of the prostate is often unrelated to the severity of LUTS. Thus, more research is needed to understand the relationship between BPH and male LUTS.

In this workshop, researchers and clinical providers considered whether BPH and LUTS are intrinsically related, or whether future research directions should consider the progression of diseases and symptoms of the bladder and prostate separately. Workshop participants reviewed the development and structure of the prostate as they relate to the risk of prostate enlargement and urinary symptoms, as well as other factors that are thought to contribute to these conditions. The workshop also provided an opportunity to examine recent advances in the understanding of prostate enlargement and its relationship to bladder dysfunction, including the roles that aging, autoimmune disease, and environmental exposures during fetal development may play in these processes.

Participants also used this opportunity to consider research priorities, such as developing new research models and imaging approaches; identifying more meaningful treatment options; and determining the necessary methods, tools, and approaches to continue making progress in this scientific area. Potential next steps would address a range of opportunities, from basic science to clinical intervention, with emphases on precision medicine approaches and patient involvement in clinical and research efforts.

A summary of the meeting is available to the public here on the NIDDK website.
Providing HOPE for a Better Way To Manage Dialysis Pain

Hundreds of thousands of Americans are living with end-stage renal disease (ESRD), also known as kidney failure. Except for a small minority who receive a kidney transplant from a suitable donor, dialysis to carry out the critical process of filtering waste materials from the blood becomes essential for life. Most often this occurs in a hemodialysis center during three 4-hour sessions each week.

The well over 600 hours each year of sitting still in a dialysis facility is a substantial burden, but very often it is not the only one: more than half of dialysis patients experience significant pain, which increases the risk for depression and lowers quality of life. Prescription opioids such as hydrocodone, oxycodone, or tramadol are often used to treat pain, including pain associated with dialysis. While often effective at easing pain, these prescription drugs also carry the risk of addiction.

As the United States grapples with the opioid epidemic, there has been renewed attention to the consequences of addiction and other side effects of this class of medications. Research showed that their use increased the likelihood of death among people treated with dialysis, and that the increase in mortality was proportional to the dose of the opioid. In 2019, NIDDK began the Hemodialysis Opioid Prescription Effort (HOPE) consortium—sometimes also known as the Hemodialysis Pain Reduction Effort—to find better approaches to managing hemodialysis-associated pain. (See insets for perspectives about the HOPE consortium from a patient participating on the study team and a clinical trial participant.)

ABOUT THE HOPE CONSORTIUM

Part of NIH’s broader Helping to End Addiction Long-term® (HEAL) Initiative, the HOPE study is testing a novel pain coping skills training intervention for people being treated with dialysis, with the goals of improving pain management and reducing opioid prescription rates in this population. The 3-month, one-on-one intervention is comprised of weekly, 45-minute telehealth sessions that employ pain coping skills training and motivational interviewing to provide a non-medical option for people to manage dialysis-related pain, comparing that to usual care. After the initial 12 sessions, the intervention provides another 12 weeks of daily, automated interactive calls designed to boost the intervention’s message and assess how the participant is doing.

Not all the people enrolled in the study are taking opioid medicines for pain, but for those who are, the therapy also provides participants with coping skills designed to decrease dependence on opioids while managing pain. After the intervention is complete, participants still taking opioids—whether or not they received the coach-led therapy—are eligible to participate in an additional observational study of buprenorphine, an alternative opioid that is generally considered safer than traditional opioids. Those who elect to receive buprenorphine are encouraged to stop taking their current opioid medication and take buprenorphine instead but are allowed to stay on their current medication if they prefer.

Both interventions together last a total of 8 to 10 months. Before and after receiving the pain coping skills training, and also after the buprenorphine intervention, the participants are asked to describe not just their pain, but also other key things that can be adversely affected by opioid use, such as how well they are sleeping, whether they can think clearly, and how their quality of life is being affected by their pain or their pain treatment. This information will help scientists determine if either or both interventions
can successfully help patients manage their pain and reduce dependence on opioids.

**PROMOTING PATIENT ENGAGEMENT THROUGH HOPE**

Importantly, HOPE is in the vanguard of NIDDK-supported clinical studies that are giving individuals with the conditions being studied a leadership role on the research team. This way, people with lived experience of these conditions contribute their voices at every stage of the research as Patient Advisors—ensuring that the work will meet the needs of the study population, developing culturally appropriate recruitment materials, helping spread the word about newly developed treatments, and more. NIDDK feels this approach will improve the science, help speed the adoption of better health care approaches, and advance health equity.

The HOPE Patient Advisors are full members of the study team, and their goal is to keep the research focused on better meeting the needs of people treated with dialysis. This approach, referred to as patient engagement, has already paid major dividends for the study. For example, the Advisors helped develop a 5-minute recruitment video, explaining the study and why people treated with dialysis who are experiencing pain should consider participating. The video and other key input from these community members have helped keep study recruitment well ahead of schedule and meeting its goal that 50 percent of study participants are Black. Although kidney disease affects people from all racial and ethnic backgrounds, the disease disproportionately affects people with African ancestry, who have historically been underrepresented in clinical research.

**HOPE FOR THE FUTURE**

The HOPE study is actively recruiting participants toward its goal of enrolling approximately 640 people at 8 clinical centers across the United States. Because of the dedication of study participants, Patient Advisors, and scientists, HOPE is poised to provide future knowledge that can benefit people with ESRD.
Dave’s Story: Helping Fellow Kidney Patients by Serving on the HOPE Study Team

Dave had a difficult decade during his 40s. Not long after he retired early from his high-pressure job, he found himself hospitalized with end-stage renal disease (ESRD), also known as kidney failure. The dialysis he received then saved his life, but the three 4-hour maintenance dialysis sessions per week he required thereafter presented difficult hurdles for him: apart from being very time consuming, even getting to the clinic was a challenge. He took public transit as far as it would go, but walking the remaining blocks was surprisingly strenuous, as he was weakened by anemia (i.e., his blood could not carry enough oxygen throughout his body). Getting home was even harder, because the procedure itself was also draining, so he was exhausted all the time. Then there was the discomfort. When Dave was asked by health care providers at the dialysis clinic if it hurt, “I’d say ‘yes.’ When they asked me where, I couldn’t pinpoint a spot. I’d just say it hurts all over.” He notes that the experience is not the same for everyone: some people treated with dialysis do experience localized pain, while others have relatively little discomfort. For Dave, dialysis kept him alive, but also meant living with generalized pain. This was particularly true during dialysis itself because the procedure required him to sit for hours in a single position.

Unfortunately, the exhaustion and pain led him to miss some dialysis appointments. After about 6 months of this, his care team called him and his wife to a meeting that would change his life. They asked why he was missing appointments and worked with him to help solve some of the logistic and financial issues that were making dialysis such a challenge for him. They also told him if he kept missing dialysis sessions he wouldn’t live much longer. It was the nudge Dave needed to take ownership of his own health: he took it as a challenge to get to every appointment on time. After a couple of months of regular dialysis, he began to feel better. “Perhaps ‘less crappy’” would be a better way of putting it, he says. Soon he began making other healthful choices—quitting smoking, eating better, exercising, and becoming stronger.

Not long thereafter, Dave accepted a role on a kidney patient advisory committee that was seeking volunteers. He says “a lightbulb went off,” as he knew some things could be done better, and so...
began a role in patient advocacy that continues today. Dave had also experienced firsthand the transformative moment when his care team listened to him, and he listened to them. As an advocate, he has had the chance to help ensure such moments happen whenever possible for others living with ESRD, and to make a difference for people in his community who need dialysis; he feels he’s “had a pretty good run as a patient advocate.” In 2015, after almost 6 years on dialysis, Dave received a kidney transplant. Since then, he has become healthier still. And—more than a decade after he retired and soon thereafter got his ESRD diagnosis—Dave was able to accept a paying job proofreading documents for a law firm.

Dave says that during his years receiving dialysis he was invited to join several clinical trials, participating in most. He says he would have been more receptive to one he declined to join if they had done a better job answering his questions about the study. So, when a scientist who had heard about his advocacy work invited him to join the steering committee for a new study to improve pain treatment in people who are receiving dialysis, he was keenly interested. (A steering committee plays an integral role by setting priorities for and overseeing research studies.) The scientist said that as a Patient Advisor and member of the Steering Committee, Dave would have a major role in ensuring the study meets the needs of its participants. Dave realized this might be another opportunity to make a difference for people with ESRD. He agreed to join, and Dave—along with others from the community of people living with ESRD—soon became an integral part of the Hemodialysis Pain Reduction Effort (HOPE) research team.

Dave recalls that at the first Steering Committee meeting, the NIDDK project scientist, Dr. Paul Kimmel, insisted Dave and the other Patient Advisors sit at the table with the scientists—as equal members of the team. “He always looks out for us. Any opportunity to make the patient voice felt, he... makes sure we have that opportunity.” Indeed, Dr. Kimmel also “challenged us [the Patient Advisors] to champion” the patient perspective. “The HOPE trial exceeded my expectations in that regard. And my expectations were high.”

Another thing he remembers from that first meeting was seeing how valuable it was to hear the differences between the perspectives of the other Patient Advisors and his own. “Not all dialysis patients think the way that I do.... I have to keep that in mind when I think about how to approach people and how to make [study] processes go better.”

“We’re all proud to be living proof of what can be done when we’re given the opportunity to contribute,” says Dave, speaking about how patient engagement has benefited the HOPE study.

As promised, the Patient Advisors are helping ensure that the HOPE study is patient centered and patient friendly by serving not only on the Steering Committee, but also the Patient Advisory Committee and the Recruitment and Retention Committee, among others. Indeed, they have played a major part in helping to guide the participant recruitment process. In a key effort, Dave and two of the other Advisors are featured in a 5-minute recruitment video on the study website, www.HOPEHDTrial.org, explaining the trial. In it, the Patient Advisors provide their own perspectives on what it is like to experience pain from dialysis, and the value of the HOPE Study. “Between the three of us we had really different takes on it, but each take was really personal—you could tell that it was just us telling our stories,” Dave says. Notably, HOPE recruitment has been faster than
expected and is meeting its goal of having 50 percent Black participants (as of the time of writing). Many of the participants cited the video as one of the reasons they joined the study. “That video has been well received,” Dave adds with understatement.

“We're all proud to be living proof of what can be done when we're given the opportunity to contribute.” Dave agrees with the NIDDK’s philosophy about patient engagement in research, saying, “if you want studies done well, we have to be at the table.” By never giving up his own hope, Dave has improved his health and life in countless ways. Through his ongoing advocacy and patient engagement work, Dave is also giving HOPE to others living with ESRD for better health and quality of life.
PERSONAL PERSPECTIVE

Leroy’s Story: Helping Fellow Kidney Patients by Participating in the HOPE Study

Leroy participated in the NIDDK-supported HOPE study

Leroy has led a life of service to others. A veteran, he retired to take care of his aging mother after years of driving a school bus, among other occupations. Leroy continues finding ways to contribute, such as by serving in the tenant council in his apartment building and being an advocate for other former servicemen and women and area seniors. He’s a consensus builder who prides himself on patience and common sense.

His mother had kidney failure, so he was familiar with the routine of dialysis. But his own diagnosis still came as something of a surprise. He had missed an appointment with his social worker at the Veterans Affairs (VA) clinic because he hadn’t felt well. When he came to the rescheduled appointment, the social worker thought that he still seemed ill. She called in a doctor—a kidney specialist who told Leroy that he had kidney failure and needed to go on dialysis right away. Leroy told them he needed to “get things straightened out” at home first, and the doctor replied “well, you be here first thing in the morning.” When he arrived the next day, the staff wasted no time starting hemodialysis.

For Leroy, like many people, dialysis was a painful experience. He recalls that when he first started going to dialysis “they would ask me about pain…. Every question has to have a scale, you know, from 1 to 10. But if you look at the question... there is no scale to it. Pain is pain…. So, when they asked ‘do you have pain? What is it from 1 to 10?’... I have to say a 10 because there is nothing else but 10.” What hurt in particular? “I was never afraid of needles, ... but the needles hurt.” (Needles are a necessary part of receiving hemodialysis, and not all methods to reduce the discomfort of insertion work for all patients.) Leroy says that it wasn’t so bad for him at first, but the repeated procedures made the area where they insert those needles sensitive. He also noted that much of the pain—especially in the shoulder of the arm with that needle in it—comes from the many hours of having to sit very still to avoid serious bleeding that could result from dislodging the needle. Eventually it wasn’t just hurting during the procedure—it was also bad enough to wake him in the middle of the night. He says that he would sometimes take over-the-counter medicines to help with pain management.

Leroy had learned from his mother’s experiences when she was on dialysis, so he knew that it was
important to pay close attention to his health care providers, and to be knowledgeable about what was going on. "I have very, very good people taking care of me there" at the VA clinic, he says. "I trust them."

That trust is one reason why Leroy was open to participating in a clinical trial that he found out about during one of his dialysis sessions at the VA clinic. One day, as he sat in the center, he was approached about participating in NIDDK’s Hemodialysis Pain Reduction Effort (HOPE) clinical trial. Leroy found out that he was eligible for the trial and was glad to participate, knowing it might help not only himself but many others with kidney failure who were undergoing dialysis and experiencing pain.

As part of the HOPE study, Leroy was randomly selected to receive a novel pain coping skills training intervention that provides a non-medical option to manage dialysis-related pain and involves one-on-one coaching sessions. He said that his participation began with a questionnaire about his experience with dialysis—his pain, and his quality of life. Later, a coach suggested strategies for dealing with pain and other challenges. Leroy says when he tried one of these strategies, “it worked, and I gave them feedback.” One of the strategies Leroy has found most helpful has been deep breaths. “This program got me doing it more. If something got on me—whether it was physically or mentally—I would stop for a minute and just take some deep breaths and blow it out.... And when I did that, my mind seemed to clear.... That helped me mentally and physically.”

He also found that the questions study staff asked him during his trial participation got him talking more openly, helping him reflect more clearly on his own needs and experiences. “Psychologically, I learned some things,” Leroy says, relating it to the Parable of the Mustard Seed, where what starts as a tiny speck grows to become so large an entire flock of birds can nest: the various HOPE pain management skills work together, becoming larger than their individual parts, and working together to combat pain. When asked if his participation in HOPE has improved his quality of life, he replies “Yes.”

“If something got on me—whether it was physically or mentally—I would stop for a minute and just take some deep breaths and blow it out.... And when I did that, my mind seemed to clear,” says Leroy, describing one of the strategies he learned about to help manage dialysis-related pain through participating in the HOPE study.

Would he encourage other people to participate in clinical research studies like HOPE? “Oh, definitely. I would give [the study] an A plus.... Give it a try.” He also said he enjoys talking to HOPE staff.

Leroy says that his perspective on his dialysis treatments has changed. “I don’t look at it as going to dialysis, now. It’s my job.... I go 3 days a week, I work 4 hours,” referring to the 4 hours that he spends on the dialysis machine at each session. On those days he is on a strict schedule: he gets up at 5:00 a.m., is out of the house at 6:30 a.m., and is on the dialysis machine at 7:00 a.m. At 11:00 a.m. he heads back home.

Dialysis is medical care that Leroy must do to stay alive because of his kidney failure. However, his decision to participate in the HOPE study represents another way that Leroy has continued his lifetime of service to others—people treated with dialysis stand to benefit from future HOPE research findings thanks to him and other HOPE study volunteers.

When asked if he would encourage other people to participate in clinical research studies like HOPE, Leroy responds: “Oh, definitely. I would give [the study] an A plus.”