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

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Acute kidney injury can cause long term damage by promoting fibrosis, which is the formation of scar tissue. This scarring process modifies genetic activity by turning genes on or off in cells. These changes can affect the kidney's ability to function properly but do not happen uniformly across all cells. Described within this chapter, researchers recently examined how two types of acute injury change the array of activated genes in cells across the kidney. In the above constructed image, cells of the injured kidney are sorted via a technique called UMAP plotting into clusters based on similar gene expression, indicated by the different colors. Cells from structures in the kidney known as proximal tubules (PT), which have three segments known as S1, S2, and S3, were found to exist in a healthy state (green clusters) or to have genetic activity consistent with injury (red), active repair (orange), or failed repair (brown). The research also identified two novel states of injury (type 1 and type 2) with distinct activation profiles that had not been previously characterized. These two subsets had metabolic changes that could differentially affect the cells' ability to repair and recover. Recognizing and understanding this heterogeneity in genetic activity following injury allows for a better understanding of specific repair mechanisms that promote healing and limit damage from fibrosis. Ultimately, this could lead to new treatments to help prevent chronic kidney disease.

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 541,000 had previously 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 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.

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 ranged from 7.0 to 7.8 percent for women and from 3.6 to 4.0 percent for men. Among those aged 18 to 64, UI prevalence ranged from 0.9 to 1.2 percent for women while the prevalence was 0.2 percent for men. 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.

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, three to eight million 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, 1.3 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.

Research on UCPPS is one example of how NIDDK is seeking a broad-based understanding of symptoms affecting the lower urinary tract (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, three to eight million 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.

UNDERSTANDING THE MOLECULAR PATHWAYS TO KIDNEY INJURY

"Kidney Atlas" Helps Illustrate Changes That Occur With Kidney Injury: Researchers have compared healthy and diseased kidney tissue at the cellular and molecular level to create the most comprehensive "kidney atlas" to date. The work, supported in part by NIDDK's Kidney Precision Medicine Project (KPMP), will help researchers delve into the mechanisms of kidney injury and healing. The kidney is a complex organ composed of multiple cell types, each of which has a specific role. Acute kidney injury (AKI) occurs when the kidney is damaged by factors such as low blood flow, certain medications, or infection. While the kidney typically continues to function following injury, some people with AKI progress to chronic kidney disease (CKD). In CKD the kidneys gradually lose their ability to excrete excess salt, eliminate waste, and balance water levels. This can lead to end-stage kidney disease, which must be treated with dialysis or may even require a kidney transplant. The atlas helps investigators understand the changes that occur in specific kidney cell populations due to different stresses and further differentiates distinct disease states to identify optimal treatment approaches.

In the study, kidney samples provided by male and female donors who were healthy or had AKI or CKD were analyzed for the types of cells present, what region of the kidney these cells were in, and how the cells adapted to their local environment. Damaged tissue was analyzed for which molecular repair pathways were turned on, what types of immune cells were present, and what cell types were communicating with each other through chemical signals. Additionally, the research distinguished pathways that led to injury resolution versus those that became "maladaptive," causing long-lasting inflammation and irreversible damage (called fibrosis). The data, available to investigators through the KPMP Kidney Tissue Atlas at www.kpmp.org, represent a collection of three-dimensional renderings and kidney maps that can help scientists from around the globe understand the kidney in health, injury, and disease.

This work could significantly improve our understanding of why some people overcome AKI while others experience a progressive loss of kidney function that develops into CKD. Furthermore, it helps distinguish distinct disease states that we now collectively treat as AKI or CKD, which could allow for more targeted therapeutics that not only halt disease progression but reverse kidney damage as well. Ultimately, KPMP research aspires to form the basis for new treatments for kidney diseases that are personalized, effective, and safe.


Probing the Molecular Events Linking Kidney Injury to Fibrosis: New research has utilized cutting-edge methods to analyze the way different types of cells respond to kidney injuries that lead to fibrosis in two mouse models of kidney injury. Acute kidney injury (AKI) often leads to chronic kidney disease—and sometimes to kidney failure—by triggering events that lead to kidney fibrosis, or scarring. Clarifying the molecular links between injury and fibrosis in the kidney might therefore suggest new and better ways to treat people with AKI to prevent long-term kidney damage.

To identify the processes involved, scientists used male mice in which one kidney was injured either by a temporary blockage of blood flow or by a temporary block of the path for urine to drain from the kidney. Using 24 kidneys from mice with one injury type or the other, they used high-throughput methods that allowed them to record details of genetic activity in over 300,000 cells, including 50 different cell types. These experiments revealed a wide variety of cellular responses in the different types of kidney injury. The animals with AKI caused by blood flow restriction were more likely to recover their kidney function than those with AKI from temporary urinary obstruction, and researchers found differences in genetic activity in various cell types that might help explain the unequal outcomes. Comparing these changes to cellular responses from other mouse models as well as human kidney disease states allowed the researchers to verify that many were relevant to human disease. Study scientists assembled their data into an atlas of genetic activity profiles of various cell types from the two injury states, which is available on the web as a useful resource for future research. This atlas is improving our understanding of the pathways that lead to kidney fibrosis and could one day lead to
treatments that help prevent chronic kidney disease from developing in people who experience AKI.


INVESTIGATING POLYCYSTIC KIDNEY DISEASE

Resolving Key Details of Polycystic Kidney Disease Genetics: Researchers helped clarify what genetic variations can cause polycystic kidney disease (PKD) by examining specific gene sequences in more than 170,000 people in a regional health care system who agreed to participate. In PKD, numerous kidney cysts form that interfere with the organ’s function. As the disease progresses it often leads to kidney failure and complications such as high blood pressure, cysts in the liver, and problems with blood vessels in the brain and heart. The most common form of PKD—autosomal dominant PKD, or ADPKD—usually occurs when someone has a disease-causing variant in either the gene PKD1 or the gene PKD2. However, although some specific variations in these genes are known to cause disease, many other PKD1 and PKD2 variants are of uncertain significance. Importantly, a significant number of people with ADPKD have been found to have only normal versions of PKD1 and PKD2, and previous research has implicated rare variants in at least 10 other genes as potentially being able to cause the disease.

New research potentially improves on scientists’ ability to predict who will develop polycystic kidney disease, and who might benefit from treatments currently in development.

To shed more light on the genetic causes of ADPKD, scientists used a technique that allowed them to zero in on the key portions of each gene previously suggested to have a role in causing the disease. They examined the gene sequences in consenting participants—more than 170,000 people—among whom 235 had a diagnosis of ADPKD. This allowed them to identify genetic variants in PKD1 and PKD2 that truly are likely to cause ADPKD—including previously unknown variations—while ruling out some of the previous suspects. Variations in PKD1 turned out to be causing the disease in a bit more than half of those with ADPKD, while PKD2 variations accounted for 14 percent, and variations in other genes accounted for an additional 8 percent. Importantly, it was not possible to identify the genetic cause of ADPKD in almost a quarter of the participants with the disease, suggesting there is much more to discover about its causes. Because 93 percent of the study participants were of European ancestry, it will be important to extend this research in a study with a more diverse group of participants. These findings potentially improve on scientists’ ability to predict who will develop ADPKD, and who might benefit from treatments currently in development.


New Technologies Help Uncover an Unexpected Role of Glucose in Polycystic Kidney Disease: Using an innovative new method to simulate a micro-environment within the kidney, scientists have discovered that glucose (sugar) absorption contributes to the growth of cysts in polycystic kidney disease (PKD). PKD is a genetic disorder that causes many fluid-filled cysts to grow in a person’s kidneys, leading to chronic kidney disease, high blood pressure, and often kidney failure. When waste products are initially filtered out of the blood in the kidney, water and important nutrients go along for the ride. These valuable materials are largely reabsorbed as they pass through tiny structures called tubules. It is within these tubules that cysts form in PKD. Because tubules are enclosed within the kidney, it is difficult to research the mechanisms behind PKD cyst formation in humans or using animal models. Previous studies have led to the development of microscopic structures outside of a living organism, called kidney organoids, which contain not only the tubules, but the other components of the blood filtration system. Importantly, kidney organoids from cells with PKD-causing mutations develop tubular cysts, just as they would in a person. Organoids are typically grown in static fluid conditions, but because of the constant exchange of fluid within the kidney, an understanding of the impact of liquid flow on PKD organoids is needed. This understanding could provide needed insight into the mechanisms of cyst formation in the kidney.

For this research study, scientists grew organoids and attached them to special microscope slides called chips that contain small channels to provide a fluid-flow environment similar to that of a living kidney. They observed via microscope that the PKD organoid cysts grew twice as fast in fluid-flow conditions as they did
when the liquid around them was motionless. The researchers discovered that cyst growth rate was closely linked to their exposure to glucose, a nutrient normally reabsorbed by the tubules. They found that the PKD cysts absorbed and expanded in response to glucose and subsequently showed that this expansion could be reversed with the use of a drug that inhibits tubular reabsorption of glucose. Equipped with the insight gained from the PKD organoid-on-chip model, the researchers were then able to confirm the uptake of fluorescent glucose in PKD cysts within the kidneys of a PKD mouse model, suggesting that the same phenomenon occurs in living PKD kidneys.

The novel organoid-on-chip PKD model used in this study provided new insight into the impact of fluid flow and glucose uptake on the formation of PKD cysts within the kidney. With further research, safety studies, and clinical trials, these findings suggest that glucose uptake-inhibiting drugs might one day help prevent the progression of PKD in people with the disease.


EXPANDING KNOWLEDGE OF KIDNEY TRANSPLANTATION

Kidneys From Deceased Organ Donors With or Without Acute Kidney Injury Show Similar Transplant Outcomes:

Findings from a national cohort study showed that kidneys from deceased donors with acute kidney injury (AKI) were not clinically different than kidneys from donors with no or resolved AKI, in terms of graft survival and function. Kidney transplantation significantly improves quality of life and eliminates costs associated with chronic dialysis, but innovative approaches are urgently needed to expand the donor pool because many people are on a waitlist and often never make it to transplant. To fill this gap, this study provides evidence for the benefits of transplanting kidneys from deceased donors with AKI, suggesting they are an underutilized resource that could help improve long-term health outcomes for those in dire need of new kidneys.

AKI is an often-reversible condition in which one’s kidneys suddenly stop functioning properly. AKI can lead to thickening and scarring of the kidney tissue and increases risk of chronic kidney disease, but whether kidneys transplanted from donors with AKI can go on to function as well as those from donors without AKI needs further research. In this study, researchers analyzed data from over 7,000 donors with ongoing AKI and over 13,000 adults who received kidney transplants from the donors from 2007 to 2016. When they compared the results to outcomes from people who received kidneys with no or resolved AKI, they did not find any clinically meaningful differences in either kidney function over 12 months or in failure rates of transplanted kidneys within 3 years. The data also showed that kidneys from donors with AKI and diabetes had slightly worse transplant outcomes, compared to kidneys with AKI but without diabetes. The researchers also found that during the study period, nearly 3,000 kidneys were discarded from donors with ongoing AKI who were under age 65 and had neither hypertension nor diabetes, suggesting that more widespread use of kidneys from potential donors with AKI could help expand the donor pool.

These findings show that even severe, ongoing AKI that persisted at the time of kidney donation does not have a significant adverse effect on transplant outcomes, and that kidneys from donors with AKI are too often discarded, needlessly limiting the pool of kidneys that could be safely and effectively transplanted into people awaiting the procedure. Continued research will be important to confirm the long-term outcomes and to increase the clinical practice of transplanting kidneys from deceased donors with AKI for those who are waiting for kidney transplants.


DISCOVERING GENETIC RISK FACTORS FOR DIABETIC KIDNEY DISEASE

A Potential Explanation for Differences in Susceptibility to Kidney Complications of Diabetes: New research in mice has identified a genetic factor that might help explain why some people with diabetes are more prone than others to kidney complications of the disease. Between 10 and 30 percent of people with either type 1 or type 2 diabetes develop diabetic kidney disease...
(DKD), making diabetes a major risk factor for loss of kidney function. But because most people with diabetes do not develop DKD, there is considerable interest in understanding what puts some people at higher risk than others. One of the early events in development of DKD is loss of a type of kidney cells called podocytes, which act as the first filter for blood. These cells permit water, salts, and other small molecules in the blood to exit the bloodstream, while blocking larger compounds like proteins from coming along for the ride. When podocytes disappear, protein levels start to fall in the blood, and rise in the urine—hallmarks of kidney disease. Podocytes also disappear in a strain of mice that are susceptible to DKD, but they remain present in a different strain of mice with kidneys that stay healthy even when the animals have diabetes. Looking for differences between the two strains, researchers noticed that the mice that lose their podocytes after developing diabetes were producing more of a protein called xanthine oxidoreductase (Xor). They found that this was due to a difference in a region of DNA that helps regulate how much of the protein is produced when glucose levels rise (as in diabetes). To see if this difference was important, the scientists created a mouse strain that had the genetic predisposition to create excess Xor but was otherwise identical to the DKD-resistant animals. When experimentally given diabetes, these mice rapidly lost their podocytes, suggesting that elevated Xor might be an important factor in contributing to DKD. If levels of Xor turn out to have a similar impact on podocytes and kidney health in people with diabetes, future work might focus on trying to develop a medication that can safely inhibit Xor's effects in hopes of one day preventing DKD or slowing its progression in those at risk for the disease.


UNDERSTANDING THE SPECTRUM OF UROLOGIC DISEASE SYMPTOMS AND TREATMENT RESPONSES

New Insights Into Overactive Bladder Urinary Symptoms: Recent findings suggest that two manifestations of overactive bladder (OAB) may reflect a spectrum of symptom severity rather than two distinct subtypes. People with OAB may experience a variety of symptoms including increased urge to urinate (urinary urgency or UU), frequent urination, urine leakage (urgency urinary incontinence or UUI), and nocturia (nighttime frequent urination). Some hypothesize that UU and UUI represent different degrees of OAB symptoms (i.e., they are the same condition), while others hypothesize that they are two separate subtypes of OAB. Though OAB is a relatively common condition, there is limited understanding of the characteristics that distinguish people with UU from those with UUI, making the clinical management of these burdensome and painful conditions challenging. Increased knowledge about these conditions could help identify if some people respond better to certain treatments, enabling a more personalized and targeted approach to treatment.

In this observational study, people with lower urinary tract symptoms who were enrolled in the Symptoms of Lower Urinary Tract Dysfunction Research Network study were characterized as experiencing either UU-only or UUI based on their answers to a questionnaire about their urinary symptoms. Of the 683 participants who reported urinary urgency at their initial visit, one-third were characterized with UU alone and two-thirds were characterized with UUI. At their initial appointment and at 3- and 12-month follow-ups, participants also answered questions to assess their urological pain, other urological symptoms, and quality of life. Individuals experiencing UU-only reported fewer symptoms like severe urgency and urinary frequency; lower levels of anxiety, depression, and stress; and better sleep and higher physical activity than those with UUI. Additionally, individuals with UUI reported a lower quality of life than those with UU alone. Interestingly, the researchers did not observe differences in urological pain between people with UU-only and people with UUI. The study investigators also observed that some people transitioned between UU-only and UUI after 12 months, whereas some improved to the point of having no urgency at all. These results suggested that UUI may be a more severe form of UU, rather than two different subtypes of OAB.

While this study provides new information about the symptoms of UU and UUI, further research is needed to definitively characterize the relationship between these conditions. A limitation of this study is that participants were followed for only 12 months. Longer observations of people with UU and UUI will provide better insight into their long-term impact on health and well-being. Further, since the population included was predominantly White, observations of more diverse
groups will help determine whether these findings apply to all people living with OAB.


Discovering the Risks of Developing Symptoms Due to Ureteral Stent Placement: Kidney stones are small, hard structures that are sometimes found in the kidneys or in the tubes known as ureters that move urine from the kidney to the bladder. When stones are too large to pass through, they can cause blockages. Physicians often recommend a surgery called a ureteroscopy (URS) in which a small tube containing a camera is used to look inside the ureters and kidneys to find, and in some cases remove, the cause of the blockage. Sometimes the surgeon may temporarily leave a tiny tube called a stent inserted in the ureters to assist in holding them open to facilitate urine flow and passage of any stones after surgery, promoting healing. Unfortunately, these stents often cause discomfort and may themselves lead to urinary difficulties in some people. However, identifying individuals who are most at risk of experiencing severe stent-related symptoms has been difficult. The NIDDK-supported Urinary Stone Disease Research Network, therefore, conducted and published the findings of the Study to Enhance Understanding of Stent-Associated Symptoms, or STENTS, with the goal of improving understanding of stent-related symptoms and risk factors for developing them.

STENTS researchers enrolled 424 people who underwent a URS and stent placement at four hospitals across the United States. Before surgery, participants filled out four short questionnaires to report pain intensity, level of pain interference on daily activities, urinary symptoms such as incontinence, increased frequency and difficulty urinating, and the level of bother due to those symptoms. These questionnaires were repeated 1, 3, and 5 days after the URS, on the day of stent removal, and 30 days after stent removal. The study researchers found that while they observed a peak in pain and urinary symptoms 1 day post-surgery with a steady decline until day 5, the level of daily interference and bother due to pain and urinary symptoms persisted longer. Surprisingly, no specific surgical factors, such as surgery length or method, were associated with higher pain and urinary symptoms or their impact. Instead, they found that painful past stent experiences were associated with higher pain intensity and interference, higher body mass index was associated with higher urinary symptoms and bother, and younger age and history of depression were associated with higher levels of all symptoms and their impact. A month after stent removal, however, all reported symptoms were below pre-surgery levels.

Researchers gained more insight into individual risk factors for pain and urinary symptoms among people with stents placed after surgery for urinary stones.

Further investigation of stent-related symptoms is needed since these results may not be broadly representative, as the study population was primarily White, and the surgeries were performed at academic medical centers. However, the knowledge gained from this study can lead to new strategies, such as options for stent-less ureteroscopies, more informed patient counseling, and new potential therapies to improve experiences of patients with kidney stones.


EXPLORING THE BIOLOGY OF BLOOD DISORDERS TO FIND NEW AVENUES FOR TREATMENT

Identification of a New Potential Therapeutic Approach to Blood Disorders: Scientists detailed a novel way to restart production of fetal hemoglobin (HbF), suggesting a new potential therapeutic approach for some blood disorders. Thalassemias and sickle cell disease are inherited blood disorders that affect hemoglobin, a protein that carries oxygen through the body. Around birth, production of HbF is turned off and shifts to production of "adult" hemoglobin (HbA). In this research, investigators studied hemoglobin genes and their regulation and identified how HbF is turned on in response to high-altitude conditions of low oxygen (hypoxia), an example of a condition in which more red blood cells are needed rapidly. This research identifies a new therapeutic approach to blood disorders of hemoglobin.
The scientists found that a protein called hypoxia-inducible factor 1α (HIF1α) can turn on production of HbF in an adult human blood cell line. Using cutting-edge molecular and genetic strategies, they found that HIF1α binds specific sequences of DNA in regions known to regulate hemoglobin genes and recruits additional proteins to stimulate production of HbF. They uncovered molecular changes in HIF1α, as well as changes in how it interacts with other proteins, that occur in the developmental switch from production of HbF to HbA. They hypothesized that reversing these changes might re-induce HbF production. To test whether this approach could be a potential therapeutic strategy, the scientists treated cells with a drug known to boost red blood cell levels. They found that treating healthy adult donor cells or cells from donors with sickle cell disease with this drug increased production of HbF to levels similar to those induced by treatment with hydroxyurea, which is used to treat sickle cell disease. Treatment of the cells from a donor with sickle cell with the drug also reduced the sickling characteristic of the disease.

The exciting finding that stabilization of HIF1α can induce production of HbF in human blood cells provides important new knowledge in understanding the regulation of hemoglobin production and indicates a potential therapeutic strategy to restart HbF production in people affected by blood disorders. Additional research will be needed to test whether this strategy can be translated from the bench to the clinic.

Lower Urinary Tract Symptoms Network (LURN): Development and Use of Improved Assessments of Urinary Symptoms

Symptoms affecting the lower urinary tract, such as urinary incontinence, frequent urination, and bladder pain, are common among adults and often have negative impacts on a person’s quality of life. Gaining a comprehensive understanding of the full spectrum of lower urinary tract symptoms (LUTS) and their impact on people dealing with them will allow for better diagnoses and development of improved treatment options.

LUTS are typically assessed using questionnaires that allow individuals to self-report and rank their symptoms, and sometimes their quality of life, via a point scale to determine their symptom severity scores. When used alongside other clinical tests and physical examinations, these assessments can help guide clinicians in their recommendations. Several questionnaires have been developed to assess LUTS, however many of them are either limited in their scope, focusing on specific disorders, or were originally developed to assess sex and/or gender-specific symptoms. For example, the American Urological Association Symptom Index was initially designed to assess symptoms of benign prostatic hyperplasia in men, while the Pelvic Floor Distress Inventory evaluates the impact of LUTS and other symptoms on the quality of life of women with pelvic floor disorders. Additionally, many of the available questionnaires do not assess the full range of LUTS.

In 2012, NIDDK established the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) with the long-term goals of better understanding different LUTS subtypes and improving measurement of patient experiences of LUTS. To achieve these aims, LURN researchers first developed the Comprehensive Assessment of Self-Reported Urinary Symptoms (CASUS), which is a 93-question survey measuring a broad variety of symptoms in both men and women with LUTS.

For use in a clinical or research setting, an optimal questionnaire must be simple and brief enough to ensure that people can fully understand and complete it, yet comprehensive enough to gather meaningful information. Therefore, using the CASUS as a starting point, LURN researchers along with a panel of clinicians used a multi-step process to develop two shorter-form questionnaires: the LURN Symptom Index 10 (SI-10) and the LURN Symptom Index 29 (SI-29). The SI-10 is primarily intended for clinical use and is composed of 10 core questions, while the SI-29, which consists of 29 core questions, is primarily designed for research. Both questionnaires cover five key symptom areas of LUTS: urinary urgency, incontinence, urination difficulty, night-time frequent
urination (referred to as nocturia), and pain. When tested for validity against commonly used LUTS measurement questionnaires, both SI-10 and SI-29 provided scores that were comparable to those of the established surveys while also providing assessment of a broader range of symptom areas.

The LURN questionnaires have already proven to be valuable resources in both research and clinical settings, facilitating assessment of LUTS symptoms and their impact on people’s lives. Several hospitals have integrated the SI-10 questionnaire into their electronic health record systems, providing clinicians with more insight into the symptoms that their patients experience.

Recognizing that addressing disparities in urological health requires ensuring these tools are accessible to diverse patient populations, LURN researchers optimized each question during questionnaire development to promote easy translation into other languages. In fact, the NIDDK-supported Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium developed a Spanish translation of the SI-10 for inclusion in its RISE FOR HEALTH study of women’s bladder health. In addition, Turkish translations of both questionnaires and a Hindi version of the SI-29 are available for download on the LURN website, and more translations are planned for the future. By making the questionnaires available in multiple languages, LURN scientists are helping ensure that their research will be both broadly applicable and widely available, thus improving comprehensive LUTS assessment in diverse communities.

More research will be necessary to fully understand and optimally treat the complex array of diseases and conditions that contribute to LUTS. Through development of the CASUS, SI-29, and SI-10 questionnaires, LURN has laid a key foundation for that work by providing comprehensive tools that are yielding new insights that may one day improve diagnostic and treatment approaches for LUTS.

For more information, visit https://nih-lurn.org/Resources/Questionnaires.
Alternatives to Race-Based Kidney Function Calculations

Race has long been used as a biological variable in health research, under the mistaken belief that racial categories correlate with genetic traits that account for population-level biological differences. However, we now know that more genetic variation exists within race categories than between them, and that race correlates poorly with the spectrum of biological variability that exists among human beings.

Accordingly, NIDDK-supported research is leading to a change in the way kidney disease is diagnosed and monitored by removing race as a variable from the equations used to estimate glomerular filtration rate (GFR). Estimated GFR remains a primary tool to assess kidney function and to classify the severity of kidney disease. Estimated GFR also helps determine prognosis and treatment, such as when hemodialysis or a transplant may be needed and how to optimize the dosage of certain drugs.

Because measuring someone’s GFR directly is expensive, difficult, and burdensome on the person being tested, GFR is normally estimated by using an inexpensive blood test to determine the concentration of a compound called creatinine. Because creatinine is synthesized at a constant rate by one’s muscles and filtered out of the blood by the kidneys, its concentration in the blood is strongly linked to kidney function. For several reasons, however, creatinine is not a perfect biomarker of a person’s actual kidney function. For example, its synthesis rate is determined by how much muscle a person has, and its blood concentration is also affected to a degree by how much meat they eat. As a result, a person’s real GFR might be a bit higher or lower than their estimated GFR, but the estimates are generally close.

However, the original study data used to develop estimated GFR calculations came overwhelmingly from participants of European descent. Subsequent work showed that the relationship between creatinine level and real GFR, on average, was the same for people from most other groups. Researchers discovered, though, that for unknown reasons creatinine levels tend to be slightly higher in Black study participants than in participants from other populations, at any given directly measured GFR. As a result, for many years estimated GFR calculations have taken into consideration whether the person being tested is “Black” or “non-Black.”

This practice is problematic. Race was created for social and political reasons, and thus has no biological basis. Indeed, race categories do not align with the continuum of human genetic and biological variability. For example, many individuals who identify as Black do not, in fact, have a higher creatinine to GFR ratio than is found in other groups. Therefore, applying the “correction factor” for Black race sometimes leads to overestimation of GFR, potentially aggravating the significant health disparities that exist in kidney health outcomes. For example, a person who identifies as Black could be erroneously excluded from receiving a kidney transplant because the equation overestimates their GFR, making it appear that their kidneys are more functional than they are. Further, the physiological reason why some Black people have a higher creatinine to true GFR ratio remains unknown, so there is no way to test for it. Thus, it is unclear who, exactly, does have a higher creatinine to true GFR ratio and thus should receive a correction factor for determination of estimated GFR.

Recent NIDDK-supported research from the Chronic Renal Insufficiency Cohort Study and the Chronic
Kidney Disease Epidemiology Collaboration has sought to address these issues by identifying new, better methods for assessing kidney function. For example, one group investigated whether genetic ancestry analysis might be useful for helping determine who the correction factor should apply to. While the use of ancestry did improve accuracy at the population level, it is both impractical and not always applicable at the individual level. Other approaches that considered body composition (e.g., how muscular a person is) or urinary creatinine excretion rates marginally improved accuracy. Another group tested an alternative formula for estimating GFR from creatinine that corrects somewhat for age and sex, but that does not use race as a modifier. On average, this approach slightly underestimated GFR for participants who identified as Black, and slightly overestimated GFR for people who considered themselves non-Black.

Encouragingly, both studies also found that estimating GFR based on blood levels of a compound called cystatin C, which does not vary by a person’s race, could help improve the accuracy of kidney function tests. One of the studies found that the most accurate, least biased results were obtained using equations that utilize both markers—creatinine and cystatin C. Thus, NIDDK-supported research has informed recent recommendations to use both serum creatinine and cystatin C to estimate GFR in adults, when cystatin C is available. Using the combined serum creatinine-cystatin C equation is particularly important when the estimated GFR value is close to a critical decision point, such as when determining drug dosing or kidney transplant eligibility.

At present, however, laboratory and reimbursement infrastructure are not yet adequate to support routine ordering of cystatin C tests in clinical settings for all people for whom GFR should be more accurately assessed. Therefore, two leading kidney health advocacy groups—the American Society of Nephrology and the National Kidney Foundation—have called for measures to improve the availability of cystatin C testing, as well as more research to find still better approaches for assessing kidney health. In the meantime, they have called for adoption of the improved creatinine-only based GFR estimation method that uses age and sex—but not race—as modifiers.

Thus, NIDDK-supported research is improving the equitable and accurate assessment of kidney function. NIDDK remains committed to research that builds on that improvement and to the overarching goal of reducing disparities in kidney disease.
Improving Kidney Stone Measurements With Automated Systems

Urinary stones, also called kidney stones, are pebble-like structures that form due to buildup of minerals from urine in the kidneys. About 11 percent of men and 6 percent of women in the United States have kidney stones at least once during their lifetime. If small enough, kidney stones can pass through the urinary tract freely, while larger stones can cause symptoms such as severe pain, bleeding, and urinary blockage. Treatment courses for kidney stones are informed by the size and location of stones and can involve simply monitoring for their passage, using methods to break them into smaller pieces, or surgically removing the stones. Reliable and precise measurement methods are therefore crucial for accurate diagnosis and treatment of kidney stones.

Multiple tests are used collectively to diagnose kidney stones, including lab tests like blood and urinary analyses to measure levels of certain minerals, and imaging tests like x-rays and computed tomography (CT) scans to visualize the location of the stones. Some stones can be missed by x-rays depending on their size and location. Therefore, CT scans, which consist of x-rays taken at multiple angles that are computer processed to produce detailed images, are more commonly used to visualize kidney stones. While CT scans are better able to detect stones, they require manual input to determine the size and other characteristics of kidney stones and to measure the anatomy surrounding them. This need for human input introduces variability and less precise measurements, as the same stone may be characterized differently from one person to the next. This variability can make it difficult to assess factors such as the likelihood of a stone passing and the measurement of changes in stone size over time. A more automated measurement process could help to ensure reliable kidney stone measurements and reduce the need for the tedious, more variable manual process.

NIDDK supports research to develop automated, more reliable measurement tools for kidney stone detection. For example, the Center for Machine Learning in Urology (CMLU), which is a joint venture of Children’s Hospital of Pennsylvania and University of Pennsylvania, aims to use machine learning with CT imaging to improve prediction of kidney stone passage. In a recent advance from the CMLU, scientists described the ability of their machine-learning algorithm to accurately measure kidney stones and compared it to the manual measurements of three different researchers. Of the 94 children and adults included in the study, both manual measurers and the algorithm were able to detect that 42 of the patients had kidney stones. However, the algorithm was shown to provide more reliable measurements of stones and regions of the urinary tract than manual input. The algorithm also had a quicker average measuring time of 12 seconds—regardless of the number of stones—compared to increased manual input times with the presence of more stones. Another NIDDK-funded program, the O’Brien Urology Research Center at Mayo Clinic, has supported the development of a semi-automated software system called qSAS. The system, which is currently in use for CT research at the Mayo Clinic and is freely available to other research groups, provides standardized stone characterization with minimal manual input.
Automated CT scan image measurement processes can lessen, and in some cases remove, the variability that comes from manual measuring, while providing more accurate assessments. Machine-learning CT imaging tools like the one developed by CMLU researchers have an added advantage of automatic continued refinement as more data points are entered. With further validation and optimization, the quicker and more reliable measurements offered by these new technologies have the potential to ensure more precise research and diagnosis of kidney stones.
Contributing to Research Toward Achieving Equity in African American Kidney Transplant Outcomes

Chronic kidney disease (CKD) is characterized by a long-term decrease in the ability of a person’s kidneys to effectively filter toxins from the blood. CKD can often lead to end-stage kidney disease (ESKD), also known as kidney failure. Treatment options for ESKD are either dialysis, which typically involves filtration of toxins from the blood by a machine, or kidney transplantation. Though beneficial, dialysis can be burdensome and draining, typically requiring 4-hour visits to a dialysis center 3 days per week. However, transplantation, if available, can provide better quality of life and enhanced survival to recipients.

African Americans experience disproportionately higher rates of ESKD compared to other racial groups in the United States. NIDDK-supported research contributed to the discovery that one factor impacting this disparity is a greater presence of specific high-risk genetic variations in the \textit{APOL1} gene among people with recent African ancestry. Two variants of this gene have been shown to account for nearly all the additional risk of ESKD in African Americans who do not have diabetes. However, it is not completely clear whether donated kidneys with two of these high-risk \textit{APOL1} variants have worse outcomes after transplantation.

To address this, NIDDK, with additional support from the National Institute of Allergy and Infectious Diseases and the National Institute on Minority Health and Health Disparities, started the \textit{APOL1} Long-term Kidney Transplantation Outcomes Network (APOLLO) in 2017. APOLLO is an observational study that involves extensive collaboration of many organizations, including the United Network for Organ Sharing, organ procurement organizations, and kidney transplant centers across the United States. The aim of the study is to determine the impact of \textit{APOL1} gene variations on outcomes of transplants with kidneys from both living and deceased African American donors. (See inset for the story of a kidney donor and kidney transplant recipient participating in APOLLO.)

**THE LINK BETWEEN AFRICAN ANCESTRY AND \textit{APOL1}-RELATED KIDNEY DISEASE RISK**

Like many other sustained genetic mutations, the variations found in the \textit{APOL1} gene likely aid in human adaptation to a specific environment. Studies have shown that the proteins of the same two \textit{APOL1} variants that result in increased risk of kidney disease likely protect people against infection with the parasites that cause a disease called sleeping sickness in humans. Scientists believe that the predominance of these parasites in sub-Saharan Africa has contributed to the high prevalence of the \textit{APOL1} variants in people with recent African ancestry.

Only people who inherit the high-risk variants from both parents appear to have increased risk of ESKD associated with \textit{APOL1}. However, most people who inherit two high-risk variants will never experience ESKD or even develop kidney disease. The mechanism by which the variant \textit{APOL1} genes lead to development of kidney disease is not fully understood, but other factors – including certain immune responses or infection with HIV (human immunodeficiency virus) might play a role.
APOLLO: ASSESSING THE INTERSECTION OF APOL1 AND AFRICAN AMERICAN DONOR KIDNEY TRANSPLANTATION

Because of the burden of dialysis treatment, kidney transplants provide people with ESKD greater quality of life. However, there are many more people who need a kidney than there are donor organs available. Unfortunately, many African American donor kidneys are not used. This occurs for a variety of reasons, including observations that kidneys transplanted from African American donors typically function for shorter periods of time and may have viral infections that kidneys from donors of other groups do not. Kidneys from African American donors are also more likely to be transplanted into African American recipients, meaning that these potential recipients are disproportionately impacted by the decreased pool of viable kidneys. If APOL1 high-risk variants among African Americans contribute to the lower rates of available kidneys, a genetic test of the donor could be used to determine the risk of kidney transplant failure instead of race. In that case, more kidneys could become available for donation, and there may be better outcomes for the recipients.

The ongoing APOLLO long-term observational study is the first forward-looking study of APOL1 and kidney transplant risk, meaning that participant outcomes and health will be observed over time instead of assessed retroactively. In APOLLO, kidney donors and recipients will be genetically tested to determine their APOL1 gene type. The outcomes of kidney transplant recipients, primarily the length of time to transplant failure, will be observed over a span of several years and assessed according to the number of donor and/or recipient APOL1 high-risk variants involved.

Although most of the kidney transplant recipients participating in APOLLO receive organs from deceased donors, some of the donors are living. As such, the study will also observe the health outcomes of these donors. Some evidence suggests that living kidney donors who have two high-risk APOL1 variants may have a higher risk of developing kidney disease at some point, long after donation. While the outcomes of living kidney donors will be observed throughout the main APOLLO study, the supplemental Living-donor Extended Time Outcome (LETO) study will assess donor outcomes as well. The LETO arm of APOLLO will look back at the kidney health outcomes of kidney donors from 15 to 20 years ago to assess any risk of APOL1 high-risk variants to living kidney donors.

Working alongside the researchers to develop and steer the study is APOLLO’s Community Advisory Council, which is made up of African American living kidney donors, kidney recipients, and their family members. An important goal of the Community Advisory Council and the researchers alike is to provide understandable education to the broad patient community. They have, therefore, collaborated to develop many videos, pamphlets, and other resources explaining the link between APOL1 gene variants and kidney disease, as well as the purpose, plans, and hopes of APOLLO. (For more information, please see: www.apollocommunity.net/community-education.) Findings from APOLLO have the potential to lead to a nationwide reworking of the current assessments for kidney donations, which could provide a second chance at life for many more people awaiting kidneys.
Deryl’s and Tanya’s Story

Transplantation Outcomes Network (APOLLO), resulted in a new beginning and a family's passion to advance health equity in kidney transplantation.

LEARNING ABOUT AND LIVING WITH CKD

Having played basketball for most of his life and now coaching a high school basketball team in Highland, Illinois, Deryl has always lived an athletic lifestyle without any other major health issues. He remembers receiving his first bit of insight into his kidney disease as a transfer student athlete at Kansas State University. "The only thing I knew was when I was in college the doctor said, ‘You have protein in your urine,’” he remembers. “The doctor said that I could have a more serious problem down the line. I was told I had [high] blood pressure also,” he says. “I was told to try and eat certain food items in moderation. It was difficult....” Overall, though, he says, “I didn’t know what it really meant and the effects that it could cause. There was no cure." Detection of protein in a person’s urine can be an early sign of kidney disease. However, Deryl did not let that stop him. He recalls telling himself, “You’re an 18-year-old young man and student athlete. Only thing that I know is all my coaches told me to play hard, and I believed playing and working hard was a cure-all.”

And that is exactly how Deryl lived a lot of his life. After college he went on to have a successful professional basketball career for over 10 years. In fact, it wasn’t until he went to his doctor for a routine exam as an Indiana State University basketball coach in his forties that he learned he had kidney damage and was diagnosed with CKD. The diagnosis was important to Deryl: “When you have a condition, it’s important to have knowledge and, if possible, treat it. In my case, I was affected by CKD on and off the court."
While kidney damage due to CKD can be slowed through lifestyle changes like blood pressure management, weight loss, and diet changes, there are currently no known ways to reverse CKD-related damage. Deryl made many adjustments to manage his CKD, although he says that it wasn’t easy. His hard work changing his diet paid off, though, and he managed to avoid needing dialysis. All of that changed when, in 2020 at the height of the COVID-19 pandemic, Deryl contracted the illness, which resulted in his ESKD.

THE LONG ROAD TO A NEW KIDNEY

Tanya, Deryl’s cousin, works as a lawyer and has dedicated her life to providing justice to her community as the head of a civil legal aid clinic in Chicago. Tanya says that as her parents’ only child, she, Deryl, and his sister “grew up more like siblings than cousins.” So, she sprang into action when she received a call from his sister saying that Deryl needed a kidney transplant. Deryl’s sister already knew then that she wasn’t a match to donate a kidney to her brother, so Tanya decided to get tested.

Matching a living donor to a transplant recipient is a complex, multi-step process. It involves tests to assess the health of both donor and recipient, determine blood type compatibility, and, most critically, to predict the chance of the recipient’s body rejecting the donor organ. Once Tanya learned she was a match, she and Deryl’s sister waited to tell him, not wanting to get his hopes up prematurely. “We just wanted to make sure that there was a plan, that I had gone through all of the education, that I had passed all the things that I needed to pass,” Tanya says.

Despite finding a donor fairly quickly, it would take over a year before Deryl could receive his cousin’s kidney. Deryl’s medical team found that his parathyroid hormone levels were elevated—a complication that can commonly occur in people with ESKD—and wanted his levels to decrease before they could safely perform the surgery. In the interim, he had to begin dialysis. “I was on dialysis for 14 months,” says Deryl. “We were not expecting me to be on dialysis that long.” He remembers the challenges of maintaining a normal life during this time: “I did dialysis from 5:00 a.m. to 9:00 a.m., and then I went to work, coached my high school team, and ran my DJ business with bookings on the weekends. And there were days that I was super weak at work and barely making it, so it was very difficult.”

In 2021, Deryl finally got the OK to undergo surgery. To Tanya and Deryl, even the date of the surgery was a good sign. “They give us a surgery date of December 1, which happens to be our maternal grandmother’s birthday,” Tanya says. “We all see this as a positive sign from God—it’s all going to go well.” Both of their surgeries did, indeed, go well. When speaking of his medical team who performed the transplant, Deryl says, “You ever seen the ‘Dream Team’ in basketball? They became my Dream Team.”

APOLLO: GAINING INSIGHT AND “CLOSURE” THROUGH KNOWLEDGE

It was in the time leading up to his kidney transplant surgery that Deryl and Tanya first learned about APOLLO. The Transplant Center at SSM Health Saint Louis University Hospital where Deryl received his transplant was a Clinical Center participating in APOLLO. He spoke to the Principal Investigator at the Center, Dr. Krista Lentine, who provided information about enrolling in the study. Speaking about his decision to enroll, Deryl recalls thinking, “Maybe I can help someone else. Maybe someone else with kidney disease.” He also says that he “started to want to know even more” regarding his kidney health.
The primary outcome measured for APOLLO is the success or failure of participant kidney transplants—as tracked by electronic medical records and the United Network for Organ Sharing—over a span of up to 4.5 years. Participant visits are infrequent and consist of an initial visit and an additional visit to collect blood and urine samples, all of which are saved in the APOLLO Central Laboratory. These samples will allow APOLLO researchers to assess secondary study measurements of kidney health, such as the presence of protein in the urine and changes in participants’ estimated kidney function.

Another important component of APOLLO is providing information and health education to the patient community about APOL1 variants and the risk for kidney disease. Though study participants have the opportunity to learn their—or in the case of deceased donors, their family member’s—APOL1 genetic results 3 to 4 years after their enrollment, they are not prevented from getting tested sooner outside of APOLLO. It was through this outside testing that Deryl learned that he had received a high-risk APOL1 variant from both of his parents. “It gave me closure,” he says, referring to now having a better understanding of the medical issues with his kidneys that he’d experienced throughout his life.

Speaking about her thoughts on the impact that APOLLO could have on outcomes for African Americans with kidney disease, Tanya says, “For me, it’s huge, because of the work that I do.” She views her participation in APOLLO and her and Deryl sharing their story as a type of justice for the African American community, saying, “Justice gets construed as what we see in the criminal justice system or in a court of law, but justice takes many forms.” She continues by saying that African Americans “have generations of not trusting our health care professionals, so I’m hoping that studies like this will give people some more agency.” The advice that she would give anyone considering donating a kidney: “Get information. Be educated about it and not so quick to assume that you know everything there is to know about donating.”

Throughout his journey with CKD and ESKD, Deryl saw the value of learning all he could about his own health. Providing his advice to anyone living with kidney disease, he says that people should learn and be informed about their own health, as it is important “to be front and center on your medical situation.” Since his transplant, he now has much more energy to do the things he loves, like spending time with his family, playing and coaching basketball, and sharing his love of music through his side job as a DJ. His days look a lot different now. “This morning,” he says, “I got up at 4:45 a.m. I played basketball from 5:30 a.m. to 7:00 a.m. I came back home... showered, went to work, got in by 7:45 a.m., worked a full day, got on the phone with you, will talk to a couple clients tonight, [my son’s] got football later today.... I’m able to power right through the day.”

The participation of Deryl, Tanya, and many others in APOLLO may one day lead to more organs for transplants, improve the health of people with ESKD, and advance health equity in kidney transplantation.