Death rates per 100,000 population are for kidney disease as the underlying cause of death, age adjusted by the direct method on the basis of the 2000 US standard population with bridged-race categories.

Source: Centers for Disease Control and Prevention
A Framingham for Kidneys

The famous Framingham Heart Study, which began in 1945, transformed our nation’s understanding of heart disease. Valuable information about risks and prevention was collected over 50 years, by tracking the health and habits of thousands of residents of Framingham, Massachusetts, and analyzing the pooled data.

Today, kidney specialists are building their own form of the Framingham study, to study some of the most pressing questions in nephrology and get answers that could aid in prevention and treatment. This year marked the end of the crucial task of gathering volunteers into the study pool, and the start of the analysis that is bound to yield important findings starting as early as 2007.

U-M nephrologist Akinolu Ojo, MD, PhD, is one of the national leaders of the Chronic Renal Insufficiency Cohort (CRIC) Study, which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases. He also heads the participation of U-M and two other local centers in the project.

The “Renal Framingham”, as Dr. Ojo calls it, is an exceptionally ambitious project, and the largest of its kind in the world. It involves 3,300 people with chronic kidney disease, many of whom also have diabetes. About half are African American, Latino or Native American, to reflect the high prevalence of kidney disease among these groups on a national level.

To help researchers learn more about chronic kidney disease, these volunteers have agreed to let study staff test their blood, their hearts, their kidneys, their urine and even their fingernails; to ask them questions; to monitor their health care patterns; and to scan their bodies—and to contact them in future years for still more tests, questions and scans. Together, the volunteers and the organizers are building the infrastructure for scores of future chronic kidney disease studies.

The CRIC study seeks answers to many questions, but especially focuses on two major puzzles: Why some people with chronic kidney disease go on to develop kidney failure that requires dialysis or transplantation, and why people with chronic kidney disease have such a high rate of cardiovascular disease.

The first question is a crucial one, because of the huge potential impact of preventing progression to kidney failure. More than 10 million Americans have chronic kidney disease, in which the kidneys slowly lose their ability to filter toxins from the blood and produce important molecules.

Diabetes is a major cause of chronic kidney disease, as are high blood pressure and certain inherited diseases. Over time, many chronic kidney disease patients will go into end-stage renal failure, with dialysis or a kidney transplant their only hope for survival.

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A Massive Undertaking

Can a tool usually used by chemists help doctors figure out why kidneys fail? New faculty member Subramaniam Pennathur, MBBS, says yes. This year, he brought his expertise with a technique called mass spectrometry to the division, and set to work analyzing the proteins and small molecules that are the hallmarks of kidney disease.

“Mass spec” as it is called, has been used by chemists for years to understand the chemical makeup of substances, from environmental samples to industrial products. But when applied to the chemistry of the human body, it may help lead to new diagnostic tests that would allow doctors to tailor a patient’s treatment to their very specific condition.

Such tests are still in the future, and will depend on the discovery of new “biomarkers” that, for example, appear in the blood of some kidney patients but not others. Mass spectrometry allows for rapid identification of potential biomarkers, both proteins and smaller compounds called metabolites.

Pennathur and his colleagues in Nephrology and the U-M’s Juvenile Diabetes Research Foundation Center for the Study of Complications of Diabetes are searching for biomarkers that might signal the early signs of diabetes-related kidney complications, which cause one-third of the cases of kidney failure in the nation. They’re also looking for molecules that could help doctors distinguish between the many causes of non-diabetic kidney failure—and catch signs of those diseases before they progress. Biomarkers could also be used to monitor a patient’s response to treatment.

This kind of research, Pennathur says, holds the potential to usher in a new age of “personalized medicine” that will replace the old model of diagnosing patients based on a few basic hallmarks. With the nation spending $20 billion a year to treat kidney failure patients, it’s a goal that can’t be reached soon enough.

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More than 350,000 Americans currently receive costly dialysis treatment, paid for largely by the federal Medicare system, to replace the function of their failed kidneys. At the current rate of growth, the dialysis population in the U.S. will exceed 10 million within the next decade unless more can be understood about how to prevent the progression of kidney disease.

Dr. Ojo and his colleagues—including U-M nephrologists Crystal Gadegbeku, MD, who chairs the national patient recruitment committee of CRIC, Rajiv Saran, MBBS, MD, MRCP, MS, and Eric Young, MD—see the study as a gold mine of data that will allow them to find out how patients who progress to kidney failure differ from those who do not. Already, more than 200 of the patients in the study have had to begin dialysis because of their disease’s progression; comparing their data with that from other patients may provide important insights.

At the same time that chronic kidney disease patients face an ever-present risk of complete kidney failure, they also face another ominous threat: a much higher than normal risk of heart attack, heart failure, and stroke. Cardiovascular disease is the major killer of patients with chronic kidney disease and many more patients with chronic kidney disease die of cardiovascular disease than ever progress to kidney failure. The link between these two life-threatening conditions is still cloudy, says Ojo, and CRIC will help get to the bottom of the mystery. It could be that the two diseases potentiate, or encourage, each other—or that they have common causes in the genetic code of DNA.
In fact, U-M nephrologists have won additional funding to mine the CRIC samples for signs of molecular markers—telltale proteins—that correlate closely with a patient’s ultimate outcome. If a particular marker in patients’ blood, for example, is found to be present among those kidney patients who later have a heart attack, and not found among those who stay free of heart disease, this information could lead to a screening test. U-M nephrologist Matthias Kretzler, MD, is leading this analysis.

Other U-M analyses will examine heart failure in chronic kidney disease patients, and calcium deposits on the blood vessel walls of kidney patients. For these, the Nephrology team will cooperate with cardiologist Kenneth Jamerson, MD, endocrinologist William Herman, MD, MPH, and radiologists Ella Kazerooni, MD, James Corbett, MD, and Anil Attili, MD.

Meanwhile, more than 560 Michigan patients will continue to travel from metro Detroit and Ann Arbor to U-M each year, for more tests and questions from research coordinators Bonnie Welliver, RN and Denise Cornish, RN. They’ll report to the General Clinical Research Center’s outpatient location at Domino’s Farms, and contribute more data to the CRIC pool.

By 2009, Ojo predicts, the CRIC project will have yielded enough data to allow researchers to launch new clinical trials of diagnostic, prevention and treatment approaches based on CRIC findings. And just as in the Framingham study, the impact on patients will reverberate for decades.

An Advocate for Kidney Research

With the National Institutes of Health (NIH) research budget tighter than ever, the biomedical and disease-advocacy communities are coming together in new ways to help raise research funds. Such was the case this year with a national kidney disease group, the Nephcure Foundation, and U-M nephrologist Lawrence B. Holzman, MD (below).

The foundation focuses on two kidney disorders that are common in children and young adults—idiopathic nephrotic syndrome and focal segmental glomerulosclerosis—that can lead to kidney failure. Dr. Holzman chairs the foundation’s scientific advisory board, and his laboratory’s research has direct implications for understanding the failure of kidney cells called podocytes in these diseases.

In May, with the NIH budget being deliberated by Congress, Dr. Holzman testified before a U.S. Senate appropriations committee to make an eloquent and urgent plea for such funding:

“Threatened by a ‘pay line’ at which only 12 to 14 percent of grant applications are funded (rather than 24 percent just three years ago), investigators have become reluctant to take risks that must be taken in their research that would dramatically advance a field,” he said. “Delays in funding outstanding proposals retard progress and result in the loss of talented and uniquely trained research personnel that cannot be readily replaced. Finally, despite NIH set asides designed to protect junior investigators, our next generation of talented young people observe the anxiety created by funding uncertainty, make career decisions based upon economic factors, and turn away from a career in biomedical science, leaving the future of this science in jeopardy.”