Twenty years of CRIC: A cohort study comes of age

13 August 2019, by Steve Graff

To date, the Chronic Renal Insufficiency Cohort study, known as CRIC, has enrolled thousands of patients. It was intended as a kidney disease counterpart to the Framingham Heart Study, which, for decades, tracked cardiovascular health in thousands of volunteers from an old factory town outside Boston. In the nearly two decades that CRIC has been running, it has taught this research community much about chronic kidney disease. Credit: Peggy Peterson

For Mark Paviglianiti, it started in 1962 when he was just six years old. While he lay in bed sick for weeks with a fever, doctors from his hometown of Lancaster, Pennsylvania, worked to figure out what was wrong. Eventually, they spotted high levels of protein in his urine—a surefire sign of kidney trouble.

They sent him to the Children's Hospital of Philadelphia, where he was put on sulfa antibiotics and prednisone. Three years later, he was off the medication and seemingly out of the woods, until his early 20s, when a kidney infection brought him back to a nephrologist. That infection, too, was fixed. Though Paviglianiti didn't feel like he had a chronic disease, these incidents began a 35-year journey of watching his kidneys and protein levels, battling other issues like a mild heart condition and high blood pressure along the way.

Such is the life of a patient with chronic kidney disease (CKD).

While it's rare for children to be diagnosed with the condition, the health problems Paviglianiti faced are exceedingly common for adults with CKD. Patients' kidneys, which rid the body of waste, progressively fail over time. Today, this complicated and highly variable disease afflicts nearly one in seven people in America, 90 percent of whom have no idea they have it because many symptoms don't typically appear until the final stage.

"Even as a young boy, my parents told me I had kidney disease, but nothing specific about it. Nor did they know how it happened," says Paviglianiti, now 62. "To this day, I don't know what triggered it."

Paviglianiti's experience, in a way, mirrors one of the largest efforts to better understand CKD. As he progressed, so did a major epidemiological study that has been running for nearly two decades.

By closely following Paviglianiti and thousands of other patients in the Chronic Renal Insufficiency Cohort (CRIC, pronounced crick) study, more than 100 researchers from the Perelman School of Medicine and other institutions have discovered new insights into CKD. Twenty years ago, researchers couldn't have predicted the paths CRIC would take, what questions they'd ask, or even the methods they'd use to answer them. Today, researchers are turning to a cutting-edge discipline and smart technologies to keep it growing.

Birth of a study

In the 1990s, before CRIC launched, many clinicians thought of kidney disease as "a binary thing, where it's like you jump off a building and nothing is happening until you hit the ground," says

Penn epidemiologist Harold Feldman, principal investigator of CRIC's Scientific and Data Coordinating Center and the study's national chair. But that binary mindset left a whole terrain of health consequences unexplored.

In the clinic, most patients either had normal kidney function or were at risk for failure. If physicians spotted a problem, typically with the urine test showing too much protein, it was diagnosed as "pre-end-stage renal disease" or worse, "chronic renal failure," which made it seem the kidneys had failed already. Clinicians would attempt to lower blood pressure and better manage diabetes, two well-known CKD drivers, but only if those problems existed. The cause of many cases was unknown. Eventually, sick patients on the edge of kidney failure prepared for dialysis or, if they were lucky, received a transplant.

During this time, CKD rates in the United States jumped significantly, with about 19 million Americans suffering in 2001, CRIC's inaugural year, according to the Centers for Disease Control and Prevention. A small percentage of cases, like Paviglianiti's, were diagnosed in children.

"All physicians knew at CRIC's start was that high blood pressure, the presence of diabetes, and protein excretion in the urine were risk indicators for CKD and its progression," says nephrologist Raymond Townsend, Penn's lead CRIC clinical center investigator and a professor of medicine. Only as recently as the late 1990s did "kidney disease" come to be recognized as "chronic kidney disease," a condition whose progressive nature was poorly understood.

In 1999, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a series of workshops, which Feldman attended and from which emerged a kidney disease counterpart to the Framingham Heart Study, that, for decades, tracked cardiovascular health in thousands of volunteers from an old factory town outside Boston. The study, still ongoing, is credited with saving millions of lives, introducing the words "risk factor" into the lexicon, and implicating cigarette smoking and high cholesterol in heart disease.

Penn and six other clinical sites were chosen to lead this new venture, with initial funding of $40 million for five years. Feldman would serve as principal investigator of the Scientific and Data Coordinating Center, along with Penn biostatistician J. Richard Landis. CRIC's charge: to better understand CKD's traditional risk factors and search for previously unknown factors for its progression and cardiovascular diseases, with an eye toward interventions to slow or stop it.

Like the Framingham study, CRIC would recruit thousands of adult patients at different stages of CKD and follow them over time to find patterns: What was the relationship between cardiovascular diseases and CKD? What else may be driving progression? Were there genetic mutations or biomarkers tied to CKD progression? New questions—and answers—branched out from there, as meaningful associations and newer research techniques surfaced.

First steps

Mark Paviglianiti, who first experienced symptoms of kidney disease at age 6, enrolled in the CRIC study in 2003. Every year, he provides samples of blood and urine and undergoes a variety of physical and mental tests to track the progression of his disease. Credit: Peggy Peterson

In the study's first phase, CRIC researchers recruited 3,600 people from around the country,

roughly 45 percent white, 46 percent black, the rest Hispanic. Half had diabetes, and 54 percent were men.

Paviglianiti was the 43rd patient to enter into the study at Penn in 2003. In his late 30s, a routine checkup revealed high blood pressure and high protein levels, so he took himself back to a Penn nephrologist, Robert Grossman. A few years later, Grossman, then a CRIC investigator, suggested he join the study, given his overall good health and his condition's state. CKD is categorized into five stages, and when Paviglianiti enrolled, he was stage 2.

During that first eight-hour study visit, the clinical research team took his blood pressure on all four limbs, along with his height, weight, and waist size. They performed an electrocardiogram (EKG) to gauge his heart health. They took his medical history and did mental tests. They extracted blood. Asked him to pee in a cup. Clipped his finger and toe nails. This happened every December, plus a phone call every six months.

"It was a great opportunity to not only learn more about myself but also for the scientific community to learn more about the disease through me," Paviglianiti says.

It wasn't long before analyses of these patients and their medical histories, using traditional statistical approaches, began revealing meaningful characteristics, or phenotypes. Meanwhile, just as CRIC began, the National Kidney Foundation published new guidelines to help physicians recognize and better define the CKD stages and other outcomes of interest beyond its progression.

On one front, CRIC confirmed what had been known: CKD disproportionately affected patients with a lower socioeconomic status and of color, and CKD patients were more likely to develop or die of cardiovascular disease (CVD). But rates of heart failure were higher than researchers expected and patients, regardless of their diabetic status, were also at a higher risk for peripheral arterial disease and stroke—patterns the CRIC researchers saw even with only five or six years of data.

For Paviglianiti, the realities of CVD risks began to crystalize four years into the study. An EKG revealed a mild condition called Mobitz 1, where the heart regularly skips a beat. That led him to Penn cardiologist Frank Silvestry, who discovered that Paviglianiti had high cholesterol, too, a known risk factor for heart problems. A statin stabilized Paviglianiti's levels. "I became more aware of the possible connection to heart-related illnesses and failure because of the CRIC study," says Paviglianiti, who was also on ACE inhibitors to control his high blood pressure.

Follow-up cohort data also told researchers that patients with a lower estimated glomerular filtration rate (eGFR) were more likely to suffer CVD events, and that the eGFR could predict their risk of having one. And longer term data offered up more precise information about blood pressure's effect on patients. CRIC study researchers, reporting in the *Annals of Internal Medicine*, found that blood pressure above 130/80 was associated with disease progression, a lower figure than what was previously believed to drive it.

"This is a space where observational outcomes, like from CRIC, in conjunction with other data, sometimes push practitioners across some treatment decision threshold," Feldman says.

Growth spurts

During CRIC's initial phase, a supplementary grant brought in 300 more Hispanic participants, moving the total to 3,900. CRIC was subsequently renewed in 2008 and 2013, eventually adding another 1,850 participants, including more than 200 at Penn and 339 more Hispanic participants in Chicago.

As CRIC grew, every December, Paviglianiti returned to Penn, providing blood and urine samples during a three-hour visit. Patients at thousands of others at sites did the same. Clinical teams would pack up their samples and ship them to Penn, where they were carefully checked in, barcoded, and filed in biobank "freezer farms."

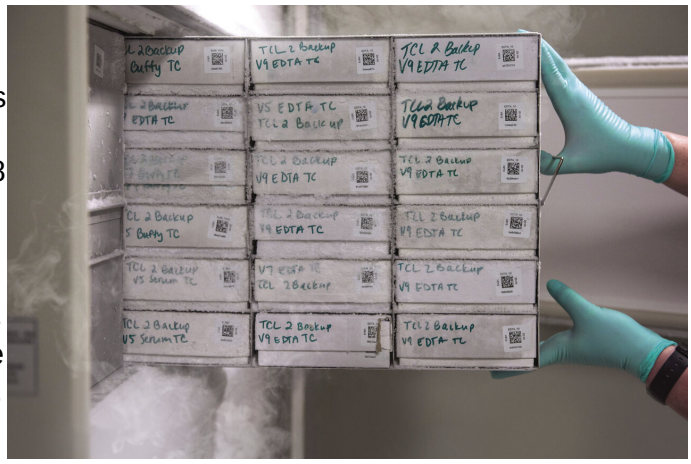
At the same time, Penn shipped thousands of samples to NIDDK's National Repository for researchers working on the parent study and on

ancillary studies. These side studies, led by CRIC and non-CRIC investigators, were funded by both the NIH and other sources. They are among CRIC's biggest strengths, adding tens of millions of dollars to the parent project, which has received roughly $8 million annually from the NIH, and expanding CRIC's footprint and contributions.

One such study from Penn found that CKD patients were more likely to have poor physical performance and became more frail as their disease progressed. In another series of studies, Penn ophthalmologist Juan Grunwald, using non-invasive, photographic tests, found that patients with damage to the retinal vasculature, known as retinopathy, had a greater chance of developing end-stage renal disease and CVD.

Cognitive decline, frailty, and retinopathy—each comorbidity not only highlights the burden of disease patients face, but can also indicate the severity of CKD, if clinicians know to screen for them early. The outcomes, for the most part, went unrecognized by the nephrology community before.

Another approach came from Townsend, who believed stiffness in large arteries was involved in the connections between high blood pressure and diabetes and some cases of CKD and related CVD. He began gathering preliminary data on arterial stiffness by measuring with technology called pulse wave velocity; that eventually led to a 10-year NIH grant. The data, published in the *American Journal of Kidney Diseases and Hypertension*, showed he was right: Stiffness in the large artery is a potent predictor of kidney disease progression, death, and cardiovascular complications.



The CRIC “freezer farm” at Penn Medicine contains more than a million specimens of blood and urine, collected over a span of nearly 20 years. Each box and each vial is individually barcoded to track its location. All these samples make it possible to keep asking questions and trying new approaches to understand chronic kidney disease. Credit: University of Pennsylvania

Next sequence

Throughout CRIC's third phase, now with a decade of data, investigators began in earnest to utilize more of the stored specimens from thousands of participants like Paviglianiti. These precious commodities were plucked out, analyzed, measured, and scanned dozens of times by industrious researchers looking for markers that may be driving the disease.

And as CRIC has grown up alongside the advent and broadening accessibility of new genetic approaches in the past two decades, researchers have found genes of interest in CKD with an evolving set of methods—from basic genotyping and DNA microarray to genome-wide association studies and epigenetic approaches.

In 2011, *JAMA* published what CRIC researchers hail as one of the study's larger clinical contributions. From a mineral metabolic marker in plasma, researchers identified a risk factor for end-stage renal disease in patients with relatively preserved kidney function, and for death in patients at all stages of CKD—it's called FGF-23, or

phosphate-regulating hormone fibroblast growth factor 23. And a seminal CRIC study published in the *New England Journal of Medicine* in 2013 found gene variants called APOL1 that could help explain the striking racial disparity in CKD progression.

The vast span of genetic and epigenetic discovery underscores another strength of CRIC: It's the repositories at both the NIDDK and Penn—which now have more than one million samples—that make these and future analyses possible.

"CRIC is best characterized as a research platform," says Amanda Anderson, a long-time CRIC investigator formerly of Penn but now at Tulane. "When [the study] was being planned and conceptualized, we had no idea that FGF-23 was something that we even wanted to measure. No one knew about APOL1. So just building the capacity for these investigations with the longitudinal follow-up is an incredible asset of the study."

New age

When the clinical research team approached Paviglianiti about remaining enrolled as one of the 3,000 patients in CRIC's fourth phase, he said yes without hesitation. The newest phase was funded by a $40 million by NIDDK award, including $17 million to Penn, extending CRIC another five years; it will have been running for 22 years when this phase ends.

"I'm hoping they see the trends, so they can piece all this together and even be able to figure out where the trajectory of this goes," says Paviglianiti, whose disease advanced to stage 4 briefly, but is back at stage 3 and being successfully managed today. His initial enrollment in 2003, and his continued enrollment in phase four, means he expects to be a CRIC participant for at least 20 years, nearly a third of his life.

For this next phase, CRIC investigators will need more frequent data on top of what they're already capturing. To do that, data collection will go mobile. Patients like Paviglianiti will receive small persistent-monitoring devices that strap onto the chest to measure physical activity and physiological parameters and to generate heartbeat data—which can, over time, point to a risk of cardiovascular and other complications.

A second device will allow patients to regularly use finger-stick blood samples to measure creatinine so the team can track kidney function. That will be in conjunction with monitoring stressors like illnesses, medications, or physical activity, for example, that researchers suspect play a cumulative role in kidney function decline. Blood and urine collection will go from once annually to 20-plus times a year. All of these data will be downloaded and fed to the team.

"We are going to have more frequent and complex detailed measures to add to what we have done so far," Landis says. "Having it all in the same study allows us to pursue questions we couldn't before."

Despite advances in understanding the CKD progression and several promising discoveries that pointed to interventions, no new disease-halting therapies have surfaced. The reality is, there is a lot still to learn about this highly variable disease. Another hurdle is funding. Compared to other diseases, overall, CKD research dollars rank fairly low, despite taking more lives than breast or prostate cancer.

To move forward, the CRIC study is using its burgeoning data and bringing a new discipline—biomedical informatics—into the fold. Many of the same questions about CKD and CVD apply, but they'll be tackled using artificial intelligence and machine learning to look for patterns in a sea of new and old data that traditional approaches can't identify alone.

"While traditional statistical analyses are very important, and still maintain pride of place here, new machine-learning methods can help inform those analyses and lead people to certain directions that they might not have thought of," says John Holmes of Penn's Institute of Biomedical Informatics, who is leading the informatics piece of CRIC's latest phase.

CRIC researchers will use tools like a topological analysis for the first time, to not only find unseen

traits, but also predict future health states of patients. "We'll essentially be mapping the progression of a disease over time—and that mapping has a certain architecture to it, a certain design," Holmes says.

Back in 2000, when the study was first designed, the researchers didn't know all the methods CRIC core teams would use or the questions they would come to ask. But the million-plus samples arriving daily at Penn for nearly two decades, all scanned, barcoded, and carefully stored, make it possible to keep asking and trying new things. And more shipments arrive every day.

30 million
number of Americans living with CKD

662,000
number of Americans with kidney failure

468,000
number of Americans on dialysis

193,000
number of Americans living with a kidney transplant

50,000
number of Americans who die from kidney disease every year

Provided by University of Pennsylvania

APA citation: Twenty years of CRIC: A cohort study comes of age (2019, August 13) retrieved 19 September 2019 from https://medicalxpress.com/news/2019-08-twenty-years-cric-cohort-age.html