In Memoriam

Honoring the Life of William Couser, Pioneer in Glomerular Disease Research

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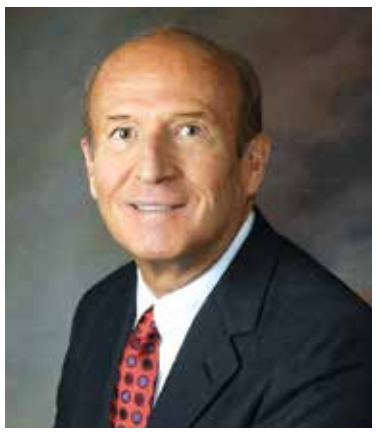

Born on July 11, 1939, in Lebanon, NH, William "Bill" G. Couser, MD, FASN, passed away on February 24, 2025, at the age of 85 (1). Deemed "one of the great academic nephrologists of the modern era" (2), Couser made significant contributions to the study of glomerular diseases. He was among the first to explore the pathogenesis of membranous nephropathy and the role of the complement system in immune-mediated glomerular diseases. His work, including the discovery that immune complexes could form in situ in the glomerulus, has been foundational in the understanding of membranous nephropathy.

Couser earned his undergraduate degree from Harvard College, going on to obtain a Bachelor of Medical Sciences from Dartmouth Medical School in 1963 and a Doctor of Medicine (cum laude) from Harvard Medical School in 1965. He completed his residency and nephrology training at top institutions, including the University of California, San Francisco, and The University of Chicago. From 1965 through 1967, Couser was a captain in the Medical Corps of the US Army, serving in Vietnam.

He was recruited to the University of Washington in 1982, where he was the Belding Scribner Professor of Medicine and led the Division of Nephrology for two decades. Under his leadership, the division became internationally recognized for research and training in glomerular diseases. Couser coauthored over 150 research publications and was instrumental in securing National Institutes of Health training grants and establishing a transplant fellowship program. Beyond his decades of seminal academic work, he was dedicated to training the next generation of nephrologists.

In addition to serving as president of ASN from 1995 to 1996, Couser served as editor-in-chief of *JASN* and was the president of the International Society of Nephrology from 2005 to 2007. Among numerous recognitions and awards, he received the John P. Peters Lifetime Achievement Award from ASN in 2018 for his contributions to nephrology.

Described by those who knew him as a "true role model for physician-scientists" (3), Couser leaves a remarkable legacy and lasting contributions to the field. ■

References

1. Division of Nephrology, University of Washington Medicine. In Memoriam, Dr. William Couser 1939–2025. Accessed March 17, 2025. https://nephrology.uw.edu/about/in-memoriam-dr-william-couser
2. Neilson EG, Johnson R. The accomplished life of William G. Couser, MD. *J Am Soc Nephrol* (published online March 7, 2025). https://journals.lww.com/jasn/citation/9900/the_accomplished_life_of_william_g__couser,_md.580.aspx
3. Salant DJ, et al. Obituary for William Couser. *Kidney Int* (published online March 12, 2025). https://www.kidney-international.org/article/S0085-2538(25)00194-2/fulltext

Kidney Scorecard Provides New Information

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"We mapped the entire genome—6 million nucleotides associated with kidney function—of each individual systematically," Susztak said. "Most of the variations that explain kidney function heritability are identified by our study."

The massive effort paid off by allowing the study to reach the so-called saturation point, of which Susztak and colleagues believe they have identified nearly all genetic variations contributing to kidney diseases. The team identified 1026 genetic variations linked to kidney function, including 97 new ones. Then, through a series of additional experiments in smaller cohorts, they explored how these mutations contribute to gene regulation, such as open chromatin, and their patterns of expression in individual cell types. Thereafter, they assembled these data into a kidney scorecard tool that other scientists can use.

"The magnitude of what [the team] accomplished was impressive," said Matthew Sampson, MD, MSCE, the Warren E. Grupe Chair of Pediatric Nephrology at Boston Children's Hospital, associate professor of pediatrics at Harvard Medical School, and associate member of the Broad Institute. "There are a lot of smart people in nephrology—physician-scientists and investigators—around the world who, given access to high-quality data such as [these], could make great inferences and really advance their discoveries. But it's a limited number of folks in the world who [like Susztak and her team] can generate this high-quality data."

Solving genetic mysteries

While assembling the genomic data of 2.2 million people was a key part of the study, it represented just a fraction of the overall work. In addition to identifying individual genetic mutations that contribute to kidney diseases, Susztak and her team also wanted to understand the role of gene regulation in contributing to kidney disease risk. She explained that 2% of the genes encode proteins, which she likens to the words in a language. The other 98% of the genome plays a role in regulating those proteins and providing a set of rules that control how they function, similar to how grammar creates a structure for words. "Most of the variations we find are not within the words but in how the words are regulated, how the words are put together," she explained.

To better understand the role of interactions between coding and noncoding genetic variants in kidney diseases, the team used kidney tissue samples from approximately 1000 volunteers to connect disease-linked noncoding variants with the coding variants that they control. Then, they used single-cell genetic sequencing to trace the effects of these variants on individual kidney cell types and began teasing out the potential mechanisms explaining how the variations may contribute to kidney diseases. "This was an enormous amount of work from many, many people," Susztak said.

The result is a three-dimensional kidney map that outlines which genes contribute to kidney diseases, where they operate, and how they cause diseases. Susztak said the work was similar to the detective game Clue, in which players try to decipher where, how, and which suspect committed a murder. "In the Clue game, geneticist version, we are looking for the same things," she said. "Who is the murderer? What is the gene? Where did the murder happen? What is the cell type? And what was the weapon? So how did the murder take place?"

Data trove

The team condensed all of the information into a kidney disease genetic scorecard to make this massive trove of data more helpful to investigators. The scorecard is searchable by gene, cell type, and chromosome. The resource is available online on Susztak's laboratory website (2). "It's a starting point," Susztak said. "Many additional data sets could be added, or [the data] could be improved. We hope to work with the [nephrology] community [to build this resource]."

Sampson anticipates that he and other researchers will use the tool to validate the results of their own human studies and to see how a gene of interest relates to open chromatin, for example. He said researchers studying kidney diseases in animal models may also use it to identify whether disease-causing gene candidates are relevant in humans.

It may also help foster drug development or repurposing of existing drugs for kidney diseases. Sampson noted that having a clear genetic mechanism is often a prerequisite for a drug company to begin developing a drug and to help it gain US Food and Drug Administration approval. "Ultimately, we're all looking to treat or cure individuals with kidney [diseases] or even prevent [them] from happening," he said. "Drugs that have a genetic justification or genetic mechanism for their action have significantly increased odds of ultimately being approved."

Susztak said she is hopeful that the scorecard will also one day help to match patients with the right therapies based on their genetic variations or to identify patients based on genetic biomarkers. She also thinks it may help identify existing drugs that could be repurposed to treat kidney diseases. She noted that there are existing drugs targeting 160 of the genes they identified. However, getting funding for the necessary studies to verify the clinical benefits of repurposed drugs can be challenging. "There are lots of new, interesting targets," she said. "I'm very, very excited about the potential repurposing of drugs, anything that could help patients. First and foremost, this is a very important first blueprint to move forward."

Susztak thanks all of her collaborators and the patients who volunteered to share their data for research. "Hopefully, this will take us to the next level," she said. "We want new therapies that improve the lives of [people] with kidney [diseases]." ■

References

1. Liu H, et al.; Regeneron Genetics Center; GHS-RGC DiscovEHR Collaboration; Penn Medicine BioBank. Kidney multiome-based genetic scorecard reveals convergent coding and regulatory variants. *Science* 2025; 387:eadp4753. doi: 10.1126/science.adp4753
2. Susztak Laboratory, Perelman School of Medicine, University of Pennsylvania. Kidney disease genetic scorecard. Accessed March 12, 2025. https://susztaklab.com/GWAS2M/