# New Cell Atlas Identifies Genetic Signature for Fibrosis

*Continued from cover*

In the study, the team used 81 human biopsy samples from 58 study participants without health problems or with hypertension or diabetes. Then, they used single-cell RNA sequencing of more than 300,000 kidney cells to map them in the kidney. They ultimately identified 44 types of kidney cells and 114 subtypes.

The researchers combined their data with data from the Kidney Precision Medicine Project (KPMP) to validate and improve the accuracy of their single-cell analysis. The KPMP published its kidney cell atlas last year (5, 6). That atlas resulted from a collaboration between KPMP and the Human BioMolecular Atlas Program. The KPMP atlas aims to help track the transition from healthy cells to kidney disease and transform kidney disease care. With hopes of spurring research by other groups and accelerating progress, the KPMP has made its data publicly available for other researchers to use.

"We were very happy that [Susztak] was able to use all 300,000 cells from the dataset to power some of her work to get more detailed cell types," said Sanjay Jain, MD, PhD, professor of medicine, pathology, and pediatrics and director of the Kidney Translational Research Center at Washington University School of Medicine in St. Louis, MO, and one of the KPMP study's (6) principal investigators. "She also used spatial transcriptomics, as we did in our atlas, focusing on some microenvironments in pathological areas," he continued.

Tapping that resource allowed Susztak and her colleagues to double the size of their dataset to include single-cell multiomic data on more than 600,000 kidney cells. Susztak explained that combining the data from multiple laboratories is essential to guard against potential biases in data generated by just one laboratory. It also helps increase confidence in their discoveries when multiple laboratories' work reinforces another. Jain agreed that having multiple laboratories working with and generating atlas data increases confidence in the results. "Collaboration is better than competition," Susztak added.

The website created to host the data from Susztak's team will provide a launch pad for inquiries by other kidney disease researchers. She explained that researchers can use the interactive tools that she and her colleagues developed to search the atlas by cell type and compare what happens in healthy kidneys or kidneys affected by hypertension or diabetes. They can also search for genes that they may be studying to evaluate where they are being expressed and how they change in disease conditions. The data are also available for download. Susztak suggested that the atlas may also be a valuable tool for clinicians in training to learn more about kidney function.

"Our paper provides a very comprehensive single-cell reference atlas for healthy kidneys and for kidneys in disease states [like hypertension and diabetes]," Susztak said. "Researchers can use this atlas like a GPS [Global Positioning System] map [of the kidney]."

## Fibrosis fingerprints

Susztak and her colleagues used AI technology to identify four distinct cellular microenvironments or neighborhoods—glomerular, immune, tubule, and fibrotic. Their atlas provides new information on the behavior and interactions of cells in these neighborhoods. "Spatial technologies can give us greater insight and perhaps help us understand not just associations [among different cells] but maybe get some insight into the mechanism of why those things go together," she said.

Susztak was particularly interested in the fibrotic niche. Her laboratory focuses on studying the effects of hypertension and diabetes, which together cause approximately 75% of kidney diseases in the United States. Some kidney diseases like immunoglobulin A nephropathy (an autoimmune condition) or focal segmental glomerulosclerosis (which causes scar tissue on the glomeruli) have specific cellular, genetic, or molecular signatures. But kidney diseases caused by hypertension or diabetes have few hallmarks besides fibrosis, she explained.

The team's AI analyses revealed a distinct gene signature in fibrotic cells associated with kidney disease progression. The results are particularly impressive because the AI algorithm did not have prior knowledge of genes linked to fibrosis, making its findings completely independent of previous research. "It told us about new genes, pathways, and interactions in the fibrotic niche," Susztak said. "We created an unbiased [genetic] signature profile that can predict patient prognosis in datasets [in which] this information is not available and then predicted patients' outcomes better than the pathologist was able to," she said.

Jain said that it is challenging for clinicians to predict which patients will develop kidney diseases. The KPMP identified signatures of kidney decline in the proximal tubule and some stromal areas that were associated with kidney function decline, which may also have some value in helping predict progression. "We are excited to see a lot of output from the community to solve this issue of categorizing patients together early on and determining whether someone will recover or progress," he said.

## Larger datasets, more insight

Susztak wants to expand the datasets for kidney mapping by spatially mapping cells from as many patients' kidney biopsies as possible and is seeking funding to achieve this goal. "We want diverse samples so the computer can learn to identify different patterns and pick out rare diseases," she said.

Growing the datasets may help AI tools pick up patient-level differences in kidney diseases, helping scientists better understand the mechanisms of different types of kidney diseases and potentially suggest new treatment targets. Identifying patient-level differences in kidney diseases may help clinicians better match existing therapies to patients' needs. For example, Levinsohn noted that physicians may be able to use the information to select an antihypertensive treatment based on what is happening in the patient's cells.

Susztak and her colleagues are currently building algorithms to help clinicians analyze patients' single-cell multiomic data and compare those data with reference samples. She explained that each patient's kidney disease is unique and that understanding patient-level differences may help clinicians to personalize care. "We are working on tools that will make [single-cell multiomic kidney data] applicable for individual clinicians," she said.

Levinsohn noted that developing and refining ways to analyze these massive datasets and extract the most important information will be another important goal for researchers in this area over the next several years. But he is hopeful that the work will help reveal the complex interactions that lead to kidney diseases and how they differ from patient to patient. "It is going to take a while and probably a few more technology improvements and data analysis improvements before we can take a look at the snapshots [provided by single-cell analysis] and tell the story in full of what it means to individuals," he said.

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Jain and his colleagues are similarly focused on building methods to analyze these growing datasets and tease out clinically important insights from the potential noise in them. The goal, he said, is to advance precision medicine for kidney diseases. "We need more datasets and knowledge base, but these [two kidney atlases] are a good initial start," he said.

Although direct clinical applications remain on the horizon, Susztak and her colleagues believe that they may be able to use this type of precision diagnostic tool to help design clinical trials or to repurpose existing drugs. "We want more and better treatments for patients with kidney diseases," she said. ■

**References**


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## Correction

The article "Paraquat Poisoning 101 for the Nephrologist" by Nikhil Saxena and Divya Bajpai published in the August 2024 issue of *Kidney News* contained an incorrect statement. The original article stated, "It has also been hypothesized that paraquat acts as a noncompetitive inhibitor of paraquat uptake at the level of the renal tubule."

**The sentence should read:**

"It has also been hypothesized that paraquat acts as a noncompetitive inhibitor of creatinine uptake at the level of the renal tubule."