Unleashing the power of data sharing to transform the drug development landscape for kidney diseases

In 2016, Barbara Gillespie, MD, FASN, Vice President and Therapeutic Head of Nephrology at Fortrea, joined a workgroup with the Kidney Health Initiative (KHI) and US FDA. They aimed to identify a proper surrogate endpoint for Immunoglobulin A nephropathy (IgAN) so that there would be a clear regulatory path toward getting drugs approved for this disease.

By 2019, the workgroup had published an article titled **Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy**, spurring new life into nephrology research and leading to more treatment options for patients. Since then, two drugs were approved (in 2021 and 2023) on the basis of this paper, which supports the FDA accelerated approval pathway.

Looking back at the last eight years, Dr. Gillespie reflected on how this unique collaboration resulted in what several stakeholders have noted may be one of the most influential papers in nephrology—and how ongoing data sharing efforts will continue to make significant changes for kidney disease patients in the future.

A brief background of IgAN

To help the body defend itself against infections, the immune system produces the immunoglobulin antibody (IgA). IgAN occurs when IgA deposits begin to accumulate in the glomeruli—microscopic networks that help filter the blood and remove waste products—leading to inflammation and scarring.

As a result of this abnormal buildup, kidney function is slowly lost and extra protein and often blood will spill into the urine. While IgAN can eventually lead to kidney failure (also called end-stage kidney disease), this chronic autoimmune disease can vary in its clinical presentation and can often be a "silent" condition as it progresses without noticeable symptoms.[1]

While IgAN is considered a rare disease in the US based on the regulatory definition of "less than 200,000 patients," it represents the most common glomerular disease in the world, largely affecting patients in Asian countries.

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Accelerating the approval of IgAN therapies

At the time of the workgroup's publication, there was no approved therapy for IgAN, even though the disease had first been recognized in 1968, and its pathophysiology, diagnostic criteria and genetic factors were further explored in the decades that followed.

"Recognizing the unmet needs for patients and the need for more clinical trials in IgAN, the KHI workgroup was formed to define a reasonably likely surrogate endpoint for IgAN to enable feasible trials in a rare disease," explained Dr. Gillespie.

By performing a meta-analysis of data from 13 clinical trials as well as epidemiologic studies, the workgroup evaluated proteinuria (a high level of protein leaking into the urine), which is a widely known biomarker of the disease. The workgroup determined that the data sufficiently supported the use of proteinuria as a surrogate endpoint in clinical trials. This finding was endorsed by the FDA given that the lead author was Dr. Aliza Thompson, Deputy Director of the Division of Cardiology and Nephrology, Center for Drug Evaluation and Research at the US FDA.

"Our efforts involved the FDA, academia and sponsors. It was an important first step to enable the accelerated pathway for IgAN clinical development," said Dr. Gillespie. "While many drugs are being tested in various glomerular diseases, the number of IgAN trials subsequently increased because our paper endorsed a clear path toward accelerated approval, thus getting drugs into the hands of patients earlier."

In 2021, just two years after our paper was published, the team's work helped advance the first drug approval for IgAN patients.

"The sponsor used proteinuria as an endpoint in their Phase III trial, following the new accelerated approval pathway," she explained. "It has been a huge incentive for sponsors to continue studying new therapies for IgAN."

Promoting data sharing to advance FSGS therapies

Since proteinuria was approved as a surrogate endpoint in IgAN, another rare kidney disease has received renewed attention.

"The FDA considers our IgA nephropathy collaboration a true success story, not just for drug approval, but also for data sharing," said Dr. Gillespie. "Now, we're also coming together to focus on another rare kidney disease: focal segmental glomerulosclerosis (FSGS)."

In this collaboration, called the **PARASOL project**, the FDA and nephrology key opinion leaders (KOLs) involved with NephCure and the International Society of Glomerular Diseases are asking researchers and sponsors to share their FSGS data for analysis. They hope to validate proteinuria (and perhaps other biomarkers) as a surrogate endpoint to facilitate the accelerated approval pathway and achieve new drug approvals for FSGS patients. Dr. Gillespie sits on the PARASOL steering committee and is the only representative from a CRO.

"I'm passionate about participating in this effort because FSGS was first described nearly 100 years ago in 1925 and still has no approved drugs," she said. "It's time to identify surrogate endpoints that support the accelerated approval pathway. Since it's difficult to enroll a lot of people in rare disease trials, data sharing is imperative to collect more data and embark on meaningful analyses."

Further work continues in IgA nephropathy as well, given the evolving data with more clinical trials being completed and published.

"While the accelerated pathway is nice because sponsors can get the drug to patients sooner, longer post-marketing confirmatory trials are still required. If we can identify endpoints to support traditional full approvals, then there is no regulatory requirement to run confirmatory trials," said Dr. Gillespie.

The next iteration of the KHI and FDA collaboration, IgAN 2.0, will kick off in March 2024 with a "Listening Session on Data Sharing" webinar for stakeholders. Dr. Gillespie has partnered with several nephrology KOLs to facilitate this session and help identify further issues related to IgAN endpoints and trial designs.

Incorporating the voice of the IgAN patient and increasing trial participation

The experiences and perspectives of patients and their caregivers represent another important facet of drug development, especially in rare kidney diseases. Dr. Gillespie often speaks to kidney patient advocacy groups (PAGs) about clinical trial participation, and she was able to attend her first in-person patient summit called **SPARK**, which is hosted by The IgA Nephropathy Foundation to share research and learn from IgA nephropathy patients and their caregivers.

"At SPARK 2023, Dr. Jonathan Barratt gave a great presentation about the two recently approved drugs (budesonide and sparsentan) and a third drug (dapagliflozin) for IgAN. Patients were thrilled to learn that they have options beyond systemic steroids, which have awful side effects," said Dr. Gillespie.

"After Dr. Barratt's talk, I gave a presentation titled 'Clinical trials are not so scary,' where I reviewed why the FDA needs clinical trials, what we do to ensure safety and the different kinds of research (beyond interventional trials) that generate data and facilitate FDA decision-making. Patients are our partners, and we cannot achieve drug approvals without their contributions that support conducting these important trials."

Dr. Gillespie is also excited about changes in the nephrology clinical practice and what it means for increasing participation.

"We're seeing a critical culture shift in nephrology to embrace trials as an option for clinical care. Participation in a disease registry and clinical trial is now recommended in our KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines in the management of patients with IgAN and other glomerular diseases,[2] she said.

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References

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