BenchtoBedside (/)

# GRIN's Power in Numbers: Three Major Pediatric Institutions Collaborate

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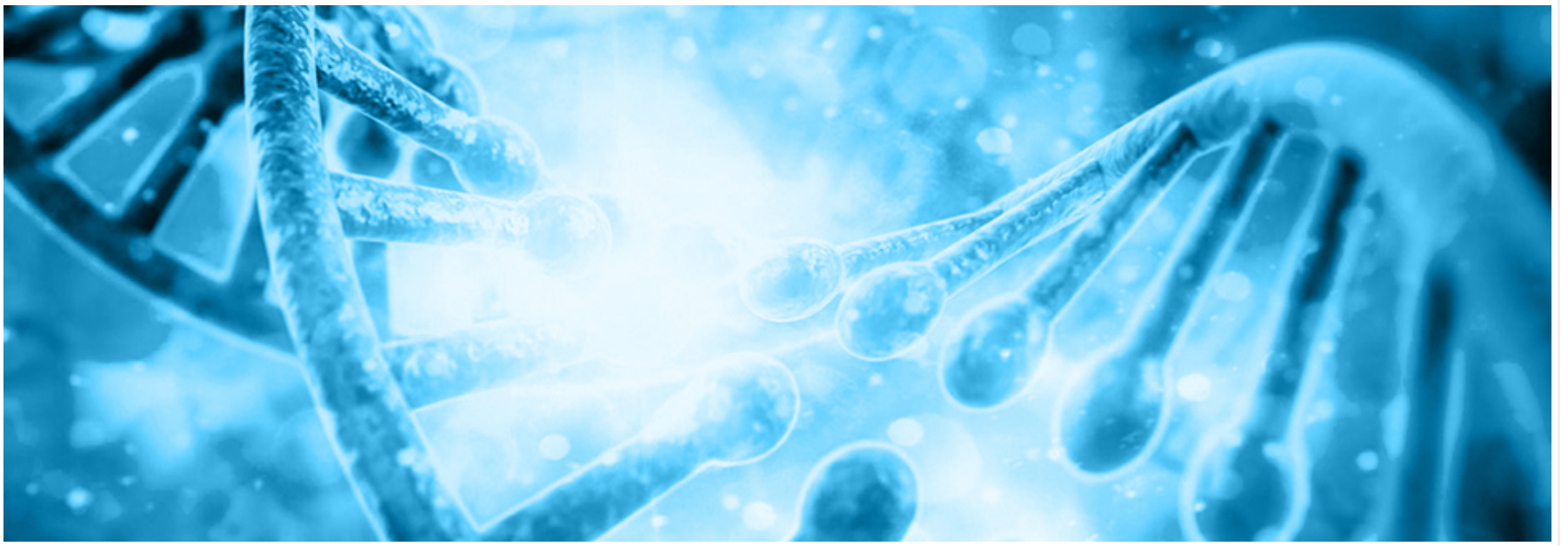

Leaders of the Genomics Research and Innovation Network (http://grinnetwork.org/) (GRIN) indeed have a lot to smile about. The groundbreaking collaborative has established an exceptional model that pools the resources of three premier pediatric academic medical institutions to accelerate genomic discovery and foster a culture of data sharing.

Going it alone to create a patient cohort population that is large enough to study can be a time-consuming process for an individual genetic scientist who wants to make a difference in a pediatric disease. That's because many pediatric diseases are so rare (https://ncats.nih.gov/rdd) that a single hospital may treat only two or three patients with a specific condition. It can be difficult to find enough patients to effectively explore these rare diseases' genetic underpinnings.

And if a researcher is interested in common disease traits that contribute to complex conditions such as diabetes or obesity, large numbers of patients are needed to participate in genetic association studies in order to magnify the statistical significance of the findings.

Recognizing that there is power in numbers, chief executive officers at Children's Hospital of Philadelphia (http://www.chop.edu/), Cincinnati Children's Hospital Medical Center (https://www.cincinnatichildrens.org/), and Boston Children's Hospital (http://www.childrenshospital.org/) contributed equal funds to form GRIN in November 2015. The concept was transformative: Begin sharing clinical and genomic data and give access to a virtual repository that their talented researchers could utilize to catalyze new projects and boost progress in pediatric genomics to advance children's health.

“The ultimate goal is to have this resource populated with over 100,000 cases that would include individuals’ clinical data at a high resolution, genotyping data, and associated biospecimens so that you can move discovery forward,” said Ian Krantz, MD (http://www.chop.edu/doctors/krantz-ian#.VOFXDfnF-So), an attending physician in the division of Human Genetics (http://www.chop.edu/centers-programs/division-human-genetics) at CHOP who serves on GRIN’s executive team.

Dr. Krantz also codirects the newly established (https://annualreport2016.research.chop.edu/accelerating-breakthroughs#new-genetics-collaborative-follows-unique-blueprint-to-individualize-medicine) Roberts Individualized Medical Genetics Center (http://www.chop.edu/centers-programs/individualized-medical-genetics-center-imgc) at CHOP. He knows well the diagnostic odyssey that families can encounter when the cause of their child’s condition is unknown. It took a decade for Dr. Krantz and his colleagues to discover that a mutation in the gene *AFF4* was behind Leta Moseley’s (http://btob.research.chop.edu/finding-new-genetic-syndrome-ends-medical-odyssey-families/) cryptic constellation of symptoms that included cognitive impairment and coarse facial features, heart defects, obesity, pulmonary involvement, short stature and abnormal bone development. They named the disease CHOPS Syndrome in *Nature Genetics (http://www.nature.com/ng/journal/v47/n4/full/ng.3229.html#close)* in 2014, and genome sequencing has since helped to identify a handful of other children (https://annualreport2015.research.chop.edu/inspiration) who have the same clinical characteristics and faulty gene. If GRIN had existed at the time when Dr. Krantz had first met Leta, arriving at that breakthrough perhaps could have taken months instead of years.

“With GRIN, we could say: ‘This is the only patient like this who I’ve seen, but does she match up with any of the other clinical phenotypes at Boston or Cincinnati?’ And if you get hits, then you might have your cohort right away to study and ask important genetic questions,” Dr. Krantz said.

Sawona Biswas, MSc, MS, CGC, a genetic counselor and CHOP’s program manager for GRIN, pointed out that another way the new initiative helps to overcome barriers to research in pediatric genomics is by addressing the problem of too much data and too little time. A wealth of data is available through electronic health records, clinical trials, and data registries, but it not feasible for individual researchers to comb through all this information and extract what they need to identify large patient cohorts with deep phenotyping. GRIN aims to make this process more consistent, precise, and seamless for its members by establishing a data trust that will allow for more comprehensive analysis of complex disease.

“Instead of working in silos, by sharing data and samples we’ll be able to collectively increase their power,” Biswas said.

Building GRIN involved many representatives — executives, clinician-researchers, program managers, bioinformatics experts, technology transfer advisers, and biobank operators, to name a few — from across all three institutions to interconnect the new shared community. The steering committee and workgroups spent much of the last year putting into place GRIN’s legal and regulatory infrastructure. They decided on memorandums of understanding, material and data transfer agreements, and institutional review board protocols so that the network members could work together.

“We’ve formed a very close and trusting relationship,” Dr. Krantz said. “We’ve built a really effective, interactive, collaborative group.”

The result is the establishment of a large cohort that includes patients who are universally consented to allow all types of their data, such as data generated by electronic health records, whole-genome and whole-exome sequencing, and imaging results, to be collected, shared, and compared consistently across GRIN sites for research purposes. Patients who participate also

agree to be re-contacted if a GRIN investigator needs additional information.

Three pilot projects tackled how different aspects of GRIN's new model would be implemented. For example, one of these projects looked at epilepsy and novel genetic causes. It enrolled 10 trios (patients and their parents) from each institution to do exome sequencing. The study team agreed on standards for the data collection. They also needed to build a cloud-based data repository and analytics platform so that the data could be accessed easily and analyzed reliably by the investigators. The other two pilot projects focused on short stature due to growth hormone resistance and childhood obesity in African-Americans.

While GRIN is getting up and running, it currently is only open to investigators at the three member institutions, but the idea is to invite other institutions to join GRIN in the future. Before any investigator dives into this unparalleled resource, GRIN's scientific committee will vet their research proposals. The network's sustainability committee also is considering how to handle commercial interest, such as from pharmaceutical companies.

"This is a very valuable resource that could be leveraged for drug discovery and therapeutic trials," Dr. Krantz said. "Having access to this type of well-characterized and accessible cohort with available biological samples is very appealing."

GRIN's planning team also anticipates that the new network will be attractive to external funding sources due to its large sample size and open data sharing philosophy. Several CHOP investigators already have shown interest in GRIN's broad data capabilities by asking for letters of support from GRIN's leadership to submit as part of their grant applications.

For Dr. Krantz, the most exciting aspect of GRIN is that it heralds a culture change in the scientific and academic world that promotes swifter discovery. He described the traditional "every man for himself" system as a slow process that offers few alternatives when a researcher reaches a dead end because of the limited numbers in a patient cohort for rare genetic conditions.

"You can accelerate discovery and breakthroughs by doing collaborative research," Dr. Krantz said. "And the reality is it's fun to collaborate … For the individual investigator who might be a little wary about sharing the samples he or she has collected, the advantage is they will have access to a much larger number of additional samples, and it opens up new questions that can be asked and propel novel discoveries."

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