When It Comes to Rare Disease, There's Power in Numbers

The Global Genes Project speaks with one voice for thousands of rare diseases that are increasingly being identified with next-generation sequencing.

Introduction

In the United States, rare diseases and disorders are defined by the U.S. Food and Drug Administration (FDA) as those that affect fewer than 200,000 people[1]. While rare, all together these diseases impact millions of people worldwide. Regrettably, their rarity translates into a dearth of clinical information about effective diagnosis and treatment, causing vast numbers of people to go undiagnosed for years[2].

With an estimated 80% of these disorders caused by gene mutations[3], next-generation sequencing (NGS) has become a valuable tool for diagnosis. The lower cost and higher throughput of NGS systems such as the Illumina HiSeq® 2500 are enabling laboratories to perform whole-genome and whole-exome sequencing to identify the presence of disease-linked mutations.

Yet, once the diagnosis is made, many families have nowhere to turn for guidance and emotional support. Fewer than half of rare diseases are supported by patient advocacy organizations.

A Friend's Crisis Sparks the Creation of a Patient Advocacy Organization

Sparked by the experience of close family friends, Nicole Boice made it her mission to fill this need. In 2000, her friends were in the midst of a diagnostic odyssey. Their son Derek was not thriving, and after two and a half years, physicians still couldn't figure out why. By chance, his physical therapist read information about Joubert syndrome, a genetic disease in which part of the cerebellum is deformed or missing. She realized the symptoms matched what she saw during her therapy sessions with Derek. After a few tests, their pediatrician confirmed that Derek had Joubert syndrome and the family finally had a diagnosis. "I couldn't believe that living in a major metropolitan area with some of the best healthcare in the world, a diagnosis could take this long," Ms. Boice said.

She began to research the incidence of rare diseases and learned that 350 million people worldwide suffer from one of 7,000 known rare diseases, most of which have genetic causes. In the United States, the incidence is one in 10, representing over 30 million people.

"In talking with families, I kept hearing similar stories," Ms. Boice added. "Numerous and sometimes painful invasive tests, multiple physician and specialist visits in cities far from home, culminating in long diagnostic odysseys that led to nowhere. We've had such success in treating diseases such as breast cancer and AIDS, yet in aggregate, the number of people suffering from rare disease dwarfs them both. Why wasn't there more of a coordinated research effort? Why were there so few resources and support for families impacted by these diseases?"

Ms. Boice leapt into action, forming the Global Genes Project, a non-profit, patient advocacy organization that collaborates with a network of about 45,000 individuals and different rare disease organizations. "We're breaking down barriers so these disease communities can communicate," Ms. Boice said. "By joining together, we can marshal a more coordinated effort to help the community at large and enable these families to share their experiences and stories, generating support to develop critical resources and drive success for these diseases."

Nicole Boice, President and Founder of the Global Genes Project.

Rick and Cristy Spooner with their daughters Calyn, Ryann, and Raelyn.

One Family's Diagnostic Odyssey

Cristy and Rick Spooner's daughter Calyn (Cali) was born in 1998. Their joy turned to concern when Cali was four months old. She began to shake her head and hands with a tremor-like movement when holding onto a bottle. Over the next few months the tremors became worse, finally resulting in what appeared to be a seizure and a trip to the hospital emergency room. Every test physicians administered, including a video EEG, came back negative for seizures. An MRI showed unusual cellular damage in part of the cerebellum, but a cerebellum biopsy was inconclusive.

At 12 months old, Cali could not sit or crawl. For several years, she received intensive therapy and while her seizure-like movements stopped, she was still far behind developmentally.

The Spooner's second daughter, Raelyn, grew into a healthy and thriving child. However, their third daughter, Ryann, began exhibiting tremor-like symptoms similar to Cali's a few months after she was born. An MRI of Ryann's brain showed the same strange pattern of cells in the cerebellum as her sister's. Multiple rounds of genetic tests revealed nothing. The Spooners began to accept that they might never know the reasons behind their daughters' conditions.

Mutual friends introduced the Spooners to Ms. Boice and the Global Gene Project. The Spooners joined several other families in sharing their stories at the organization's inaugural Tribute to Champions Gala, an outreach event to honor physicians and other members of the medical and scientific community for the strides they're making in rare disease research.

Coincidentally, one of the medical geneticists they had worked with several years earlier was also in attendance. She told them about a new test, whole-exome sequencing, that she believed might enable her to diagnose Cali's disorder. The Spooners agreed and for what seemed to be the hundredth time, Cali and Ryann's blood was drawn. The samples were sent to Ambry Genetics, a CAP*-accredited and CLIA**-certified commercial clinical laboratory that uses HiSeq systems to perform sequencing analysis. This time, the results came back with "POSITIVE" printed on the report. The cause of Cali and Ryann's illness was a mitochondrial disease known as Complex I[4]. Each inherited the same recessive gene from their parents. "According to our doctors, it is more common to win the lottery twice than it is to meet someone with the same recessive gene," Mr. Spooner said.

Whole-Exome Sequencing Moves to the CLIA Laboratory

While Complex I disease accounts for up to 30% of the mitochondrial disorders identified in children, it is characterized by significant clinical and genetic heterogeneity, making it difficult for clinicians to diagnose. Over the last two years, the availability of high-throughput, cost-effective whole-exome sequencing has enabled clinicians to identify the causative mutation in large numbers of patients[5]. Fortunately, the Spooner's medical plan covered the cost of whole-exome sequencing and analysis, but many plans do not. Recently, the Translational Genomics Research Institute (TGen) opened a CLIA laboratory to validate whole-genome, exome, and transcriptome sequencing protocols on the Illumina HiSeq 2500 system[6]. Through its Center for Rare Childhood Disorders it is making the case to third-party payers that exome sequencing and transcriptome analysis are cost-effective tests for specific conditions, and studying both can improve the diagnostic rate.

Enhancing Physician Awareness of Rare Diseases

Clearly, third-party payers aren't the only group that need to become more informed regarding rare disorders and the value NGS offers in identifying them. Most physicians have limited real-world experience in treating rare diseases because they are so uncommon.

The Galas are but one way that the Global Genes Project reaches out to physicians. As a member of its external advisory board, Ms. Boice joined thought leaders in the medical, health policy, and health economics fields in contributing to the Rare Disease Impact Report developed by Shire PLC to identify the health, psycho-social, and economic impact of rare diseases on patient and medical communities in the United States and the United Kingdom. Distributed at the World Orphan Drug Congress in Washington, DC, the report seeks to raise awareness of these diseases among the physician and patient communities.

Growing Investment in Rare Disease Research

With NGS becoming more cost-effective, the prospect of sequencing newborns at birth is edging toward reality. The opportunity to understand the information in each sequence and use it to identify rare disease is something the National Institutes of Health (NIH) has already started to consider.

In 2009, NIH launched the Therapeutics for Rare and Neglected Diseases Program with initial funding of $24 million to fuel an integrated drug development pipeline to produce new treatments for rare and neglected diseases[7]. In 2012, the agency initiated the Undiagnosed Diseases Program (UDP) to provide a new network of medical research centers focused on the discovery, diagnosis, and care of undiagnosed patients by capitalizing on recent advances in genomics and the infusion of basic researchers in clinical projects[8].

"When Francis Collins took over the NIH he flipped the paradigm for disease research funding," Ms. Boice said. "In the past, most of the research dollars were spent studying common diseases, with the hope that discoveries there would trickle down and lead to a better understanding of uncommon diseases. Today, more NIH research is being conducted on rare diseases and disorders and it is actually having a trickle-up effect."

Hope for Tomorrow

Now 14 years old, Cali can stand on her own for a minute and take about five steps before needing assistance. She cannot speak clearly and suffers from extreme cognitive delay. Ryann can walk about 10 feet on her own. Yet there is hope.

The Spooners see themselves as beneficiaries of the genetic information provided by NGS systems. "The diagnosis has been life-changing," said Mr. Spooner. "Our huge question mark exploded into tiny pieces and has been replaced by a name—Complex I deficiency. The great news is that there is a treatment available, a program of vitamins and an eating regimen that might help their development."

Ms. Spooner said family members experienced a tremendous sense of relief after they learned the results. "It was a weight lifted off our shoulders. After 14 years, we finally have an answer. We're now part

*College of American Pathologists

** Clinical Laboratory Improvement Amendments

of the mitochondrial disease community and we've already started to meet and talk with other families with children suffering from these diseases."

In the last four years, momentum has built around rare disease, primarily due to technology innovations such as Illumina sequencing. "Illumina technologies have the potential to transform the lives of undiagnosed patients by identifying the diseases that afflict them, and enabling their physicians and parents to build a roadmap for their care," Ms. Boice stated. "Genetics is opening up a whole new world for these families, providing them with the answers they seek."

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