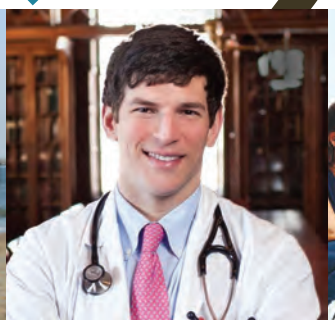
# NEXT:

## IMAGINING THE FUTURE OF RARE DISEASE

Global Genes®
Allies in Rare Disease

# NEXT:

# IMAGINING THE FUTURE OF RARE DISEASE

Daniel S. Levine

September 2019

# A LETTER FROM THE FOUNDER

**Nicole Boice**
**Founder, Global Genes**

As Global Genes approached its tenth anniversary, we wanted to take the opportunity to not only look back and reflect upon how far we had come, but also to look ahead and think about how the rare disease community could capitalize on the range of opportunities before us now and on the near horizon. The report that follows is a concise examination of the road ahead, informed by the path behind, and the insights of luminaries from science, technology, medicine, and the rare disease world.

People faced with rare diseases are an impatient group because they have to be. Time is a luxury patients and families can't afford, and ten years is sadly more than a lifetime for many. As such, even the dizzying pace at which scientific advances are being made today can still seem plodding to the thousands of rare disease communities without approved treatments.

But there is hope. We've experienced major leaps forward within the last decade. Since our founding, for example, we've seen great improvements in the precision, availability, and affordability of DNA sequencing. Gene therapy—where progress had stalled a decade ago—is now at the forefront in potentially treating or curing a number of rare diseases. We've experienced the integration of game-changing technologies like artificial intelligence, into the diagnostic and drug development process, and the approval of a growing number of therapies that, rather than simply treating symptoms, act on the underlying causes of rare diseases.

The pace of innovation continues to accelerate, thanks in no small measure to the growing sophistication of rare disease patients and their families, who have pushed beyond advocating and raising funds for basic research to the point where a growing number of leaders and communities are now playing a critical role in advancing drug discovery, translational research, and drug development.

In undertaking this report, we sought to take a wide view of the rare disease landscape and to look at how technology is improving the ability to understand, diagnose, develop treatments, and deliver care to patients. Though most rare diseases remain without an approved treatment and most patients still face a protracted diagnostic odyssey, there is reason to believe dramatic changes are within our grasp.

While there are technological advances that promise to transform the rare disease landscape, our discussions with patient advocates, researchers, drug developers, and other stakeholders in the world of rare disease made it clear that our ability to overcome scientific challenges will in itself not be enough. If we are to fully realize the opportunities before us today, we must be innovative in the way that we approach business, finance, organizational development, delivery, regulation and access issues as well.

We hope this report begins an ongoing discussion in the years ahead to foster creative thinking and new approaches to solving a range of problems that may stand in the way of patients getting the answers and care they need.

Always in hope,

Nicole Boice
Founder
Global Genes

## Introduction

# THE FIGHT FOR TOMORROWS

> **"These concepts are no longer the stuff of science fiction."**
>
> *—Scott Gottlieb, then-FDA commissioner in a November 2017 statement issued with a set of guidance documents relating to regenerative medicine*

Bertrand Might was born to Matt and Cristina Might on December 9, 2007. By the time he reached three months of age, his development had slowed. By six months, he had little motor control. His parents described him as "jiggly," and they began a diagnostic odyssey for Bertrand. The infant seemed to be in constant discomfort. They would later learn Bertrand suffered from frequent seizures. He also didn't produce tears, an issue that caused progressive damage to his corneas. As doctors conducted more tests over time, they discovered new symptoms and ruled out known conditions.

In April 2009, Matt, Cristina, and Bertrand traveled from their home, at that time in Utah to Duke University in Durham, North Carolina, to meet with a team of scientists there. As part of their effort to diagnose him, the researchers performed whole genome sequencing on him and his parents. Three years after first meeting with the Duke team, the scientists told the Mights that Bertrand had a mutation of a gene known as NGLY1, and that they believed it was responsible for his condition. The pathogenic variant Bertrand has results in a metabolic disorder. Because of his mutation, Bertrand is unable to produce needed amounts of the enzyme N-glycanase 1, which removes sugars from proteins and plays an essential role in clearing metabolic waste from cells. As a result of this deficiency, over time, fragments of sugar collect in cells throughout the body and impede function. Matt and Cristina each carry a different NGLY1 mutation. Even though they each produced half of the normal levels of the enzyme, they both had adequate amounts of it for their cells to function unimpeded. The Duke scientists believed they had zeroed in on the single cause of Bertrand's complex and many symptoms but could not be sure. They also believed Bertrand was the first patient with NGLY1 deficiency to have been discovered. To be certain, they needed to find other people with NGLY1 mutations to see if they manifested symptoms similar to Bertrand's. Matt Might asked what every parent of a child asks when confronted with a rare disease diagnosis: "What do we do next?"

In May of 2012, following Bertrand's diagnosis, Matt Might published a blog post on his personal website with

the headline “Hunting down my son’s killer.” Might began his post with a provocative statement. “I found my son’s killer. It took three years. But we did it,” Might wrote. “I should clarify one point: my son is very much alive. Yet, my wife Cristina and I have been found responsible for his death. My son Bertrand has a new genetic disorder.” If Bertrand’s diagnosis was to be confirmed, they would need to find other people with NGLY1 deficiency. What’s more, if they were to have any hope of engaging researchers in an effort to understand Bertrand’s condition and find possible treatments, locating other patients and their families would be essential.

The post wasn’t intended to be a confessional, or a psychotherapeutic exercise. It was meant to serve as a beacon for any parent who was given a similar diagnosis and entered NGLY1 into a Google search. The diagnostic odyssey for the Mights produced a suspect gene, but the mutation was believed to be so rare that the team at Duke told the Mights it could be 10 or 20 years before they found another patient with the same mutation as Bertrand’s.

The post went viral. Within two weeks, they had found a second patient with an undiagnosed condition where NGLY1 was considered a possible underlying cause of a child’s symptoms. Next, two patients in Israel were found, and then another in the United States. It continued from there. Today, more than 60 patients have been identified from around the world. The families of these children keep in close contact, are conducting a natural history study with the National Institutes of Health, and are working to secure funding for a clinical trial. “What started with a blog post,” said Might, “became a brand-new disease community that has formed a powerful infrastructure for the science of the disease.”

**The Might family**

**"What started with a blog post became a brand-new disease community that has formed a powerful infrastructure for the science of the disease."**

*—Matt Might, whose son Bertrand was the first person diagnosed with NGLY1 deficiency*

## The transformation of the rare disease landscape

The Mights' story is repeated all too often in the world of rare disease when patients and their families are confronted with a rare disease diagnosis. They try to understand what the diagnosis means, find others with the same condition, and figure out what to do next. Though these conditions by definition affect small populations, collectively they take a large toll.

The numbers around rare diseases are imprecise. Though they are often stated as fact, a range of numbers are used often without any explanation of the source of those numbers or the basis for them. A rare disease is defined in the United States as a condition that affects fewer than 200,000 people. Based on global health organizations, government estimates, and pharmaceutical industry sources, there are roughly 6,000 to 8,000 known rare diseases, an estimated 80 percent of which have an underlying genetic cause. More than half of these conditions affect children and many of them are deadly. About 30 percent of children afflicted with a rare disease will die before the age of five. Despite the considerable progress that has been made in understanding rare disease, about 95 percent of the rare diseases that have been identified to date are without an approved treatment. About 30 million people in the United States—nearly one in 10 people—suffer from a rare disease. Globally, an estimated 400 million people are afflicted with such conditions.

In addition to their physical and financial impact, rare diseases take a significant emotional toll on patients and their families. This is compounded by a lack of information and a lack of support for patients and caregivers. A 2013 **report** from the pharmaceutical company Shire (now Takeda Pharmaceutical) on the impact of rare diseases found more than 80 percent of patients in the United States and United Kingdom who responded to a survey for the study expressed feelings of anxiety and stress, and about 70 percent said their condition caused them to have less interaction with family and friends. Nearly three-quarters expressed feelings of depression.[1]

The small population of patients that individual rare diseases affect has historically posed challenges for developing the type of understanding necessary to diagnose these conditions in a timely manner, understand the often heterogeneous manifestations and progression of a disease, engage researchers to determine the biological mechanisms underlying a given rare condition, and entice drug developers to invest the time and money necessary to develop therapies.

That began to change in 1979 with a **report** from the Interagency Task Force on Significant Drugs of Limited Commercial Value, a panel of representatives from the U.S. Food and Drug Administration (FDA), the National Institutes of Health, academia, and industry.[2] "Many significant drugs essential for diagnosis or treatment are not available mainly because research, development, and production are deemed too expensive relative to expected economic return," the report said. "As a result, important groups of patients, some critically ill, and scientific efforts devoted to rare or exotic conditions receive no support from either public or private resources." To address the matter, the report called for several administrative, economic, scientific, and legal incentives. It represented a significant step toward the passage of the Orphan Drug Act of 1983.

**"The drug company's blockbuster models have failed, and they have decided that they need a new model."**

*—Sharon Terry, president and CEO of Genetic Alliance*

The Orphan Drug Act and subsequent amendments are widely credited with stimulating investment in the development of drugs to treat rare diseases. The law provided drug developers who brought a rare disease therapy to market seven years of marketing exclusivity, the ability to interact with the U.S. Food and Drug Administration during the drug development process, and a 50 percent tax credit on research and development expenses relating to these therapies. Under the Trump Administration's 2017 tax reform legislation, the tax credit was cut to 25 percent of R&D expenses. Before the passage of the Orphan Drug Act the FDA approved just 34 treatments for rare diseases. Since then, the FDA has approved more than 600 new therapies to treat orphan disease, according to a February 2019 tally by the Biotechnology Innovation Organization (BIO). In 2018, 34 of the 59 novel drugs the agency approved carried orphan designations.

| Orphan Drugs by the Numbers | |
|---|---|
| Number of companies developing orphan therapies | **595** |
| Number of orphan therapies approved | **695** |
| Number of orphan therapies approved for oncology | **254** |
| Number of rare diseases with approved therapies | **302** |
| Number of approved therapies BIO calls cures | **12** |

*Source: Biotechnology Industry Organization, December 2018*

The passage of the Orphan Drug Act had an unintended effect. As Mary Dunkle, the former vice president of communications for the National Organization for Rare Disorders, noted in a 2014 **article** in the journal *Orphan Drugs: Research and Reviews*, it catalyzed the rare disease patient advocacy community and taught advocates how to work with lawmakers, the press, and each other. "Just before the Orphan Drug Act was enacted, the members of the patient coalition, all of whom represented disease-specific patient communities at that time, recognized that the Orphan Drug Act might never have become reality if they had not focused on their common ground and worked together to provide advocacy for it," she wrote as she discussed how that led to the formation of the National Organization for Rare Disorders, or NORD. "They realized, as NORD's slogan states today: 'Alone we are rare. Together we are strong.'"[3]

In addition to catalyzing drug development among industry participants and awakening patient advocates to the collective power they could have, scientific developments also set the stage for the dramatic advances that have driven new understandings of the basis for rare genetic diseases and how to diagnose and cure them. At first, pioneering enzyme replacement therapies helped change the business case for pursuing rare diseases. With the mapping of the human genome, the advent of low-cost sequencing, and the emergence of therapeutic modalities that can disrupt, edit, and correct the behavior of faulty genes, rare diseases are today at the forefront of an emerging era of genetic medicine.

"The biggest piece of progress has actually nothing to do with what we all have done in terms of activism, and that is that the drug company's blockbuster models have failed, and they have decided that they need a new model, and they're going to go after rare diseases because they garner such enormous amounts of money when you find the right drug," said Sharon Terry, president and CEO of the advocacy organization Genetic Alliance.

"The biggest progress I've seen is every single pharmaceutical company opening a rare disease division, and the incredible attention in the market from venture money for rare diseases, as well as new startups."

## A unique moment

Matt Might's blog post reflected both the limits and power of technology with regards to the issues rare disease patients and their families face. While the emergence of sophisticated technologies is enabling scientific feats that seemed unimaginable a generation ago, they still have their limits. In the case of Bertrand Might, genetic testing allowed for a diagnosis, but on its own could not provide a definitive answer. At the same time, two of the most transformational technologies that have driven advances in the rare disease sector have been the Internet and the advent of social media, which have put the ability in the hands of rare disease patients and their families to connect, collaborate, and drive research. It was a simple blog post that allowed Matt Might to find other patients and not only obtain a clear diagnosis but form the genesis for a patient community that together is driving research forward and working to develop potential therapies.

We are living in a time when an array of technologies promises to transform the way rare disease patients are diagnosed and treated. The convergence of information technology and biotechnology, the movement of low-cost sequencing into clinical use, and the incorporation of artificial intelligence throughout the rare disease continuum are accelerating improvements to research, diagnosis, and care for patients. The proliferation of low-cost wearable sensors and cameras has transformed smartphones into ubiquitous tools that can be harnessed to monitor patients with chronic conditions. And the emergence of targeted and regenerative therapies to not only treat, but functionally cure rare genetic diseases, has fueled new hope among rare disease patients for a brighter future in which they may be free of their conditions.

"These concepts are no longer the stuff of science fiction," FDA commissioner Scott Gottlieb said in a November 2017 **statement** issued with the release of a set of guidance documents relating to regenerative medicine, "but rather, real-life science where cells and tissues can be engineered to grow healthy, functional organs to replace diseased ones; where new genes can be introduced into the body to combat disease; and where adult stem cells can generate replacements for cells that are lost to injury or illness."[4]

This report seeks to capture the range of technological developments and innovation that is propelling advances in the rare disease space. It is by no means all-inclusive but meant to suggest the range and rapid pace at which science and technology are moving, the transformative nature of the changes that are being brought about, and the potential to radically alter how a decade from now someone with a genetic disease will be diagnosed and treated. Though it considers the rare disease continuum in four broad categories of diagnosis, research, therapeutic development, and treatment, the nature of rare disease today blurs the lines between these areas. This report also seeks to consider some of the challenges and obstacles existing today that may hamper our ability to capitalize on the potential before us to end the diagnostic odyssey, speed discovery, and bring new treatments and cures to patients. While scientific challenges remain, there are financial, policy, and man-made barriers that arise when large numbers of organizations and individuals with competing interests try to address complex problems. What was true in the past will be true in the future. The greatest success will come when people work together toward common goals. ■

**The greatest success will come when people work together toward common goals.**

# THE ODYSSEY

**"The moment of diagnosis, understanding what your family member has, is extremely important, even if there's no treatment. It is a moment where you finally reach the end of one journey. You still have a lifetime of taking care of your family member, but at the very least, your disease has a name. You start understanding what you're facing, you start understanding diagnosis, you start understanding potentially the management of this disease. Putting a name on a disease is extremely important for the family."**

*—Dekel Gelbman, CEO, FDNA*

Ryan Taft was trained in genomics and computational biology. He had gone to the University of Queensland in Australia to work on his doctorate. He was focused on understanding how genes are turned on and off and he was particularly interested in so-called "junk DNA"—vast stretches of the genome that had no apparent function. It was during this time that a general practitioner, whom Taft's wife knew, asked if he would be willing to talk to the father of one of his patients who appeared to have a genetic condition but needed help making sense of the results he now had from whole genome sequencing.

Taft agreed to speak to the man, Stephen Damiani. Damiani's son Massimo was quite ill. Taft intended to talk for about half an hour and offer what advice he could about how Damiani might go about finding the people he needed to help analyze the data he had. Damiani had other plans. By the time the call ended an hour-and-a-half after it began, the father had enlisted Taft in an effort to solve the genetic puzzle of Massimo's illness.

Massimo was born in 2008. He began to regress around age 1. An account from his father posted on Mission Massimo Foundation's **website** said his legs and ankles were stiff, he had trouble with balance, and he kept thrusting his head back. He had been born with a single kidney and had spinal problems that were being watched since he was a month old. An MRI revealed an abnormality. Massimo appeared to have a leukodystrophy, a rare neurodegenerative disorder.

**"If the answer is, 'Yes,' run a genome and then let the genome do the talking in terms of identifying changes in the DNA that look like they're not right."**

*—Ryan Taft, vice president of scientific research for Illumina*

Doctors performed tests to identify the specific disorder that afflicted Massimo, or at least rule out others. All through this time, Massimo continued to deteriorate. He would choke while eating and drinking, lost what vocabulary he had, and soon was unable to crawl or sit. Damiani believed that if there was any hope of finding a treatment for his son, it would need to begin with a diagnosis.[5]

One specialist in Holland suggested to Massimo's doctor that the boy might have a condition known as vanishing white matter disease, although his presentation didn't seem to fit. Genetic testing would be necessary, but his private health insurance didn't cover the $10,000 test for vanishing white matter. Damiani decided instead of doing the specialized test, he would pay out-of-pocket for whole genome sequencing using a subsidized program through Illumina Inc., which would cost about the same. He found a local genetic service that would use the whole genome sequencing data to rule out the known genes for vanishing white matter disease.

With Massimo's genetic data in hand, Damiani at the end of 2010 reached out to the National Center for Genomic Research in the United States, which agreed to analyze it. The analysis revealed 11,500 genetic variants, too large a list of suspects to be meaningful. Damiani needed to weed down that number. "Our search for a diagnosis has now become a research project," wrote Damiani, "but we didn't have researchers."

A patient with a rare disease will visit an average of 7.3 physicians and it will take 4.8 years from symptom onset to an accurate diagnosis, according to a **survey** of patients, family members, and healthcare professionals conducted on behalf of Global Genes that was published in the *Journal of Rare Disorders* in 2014.[6] Because rare diseases can often present with symptoms associated with more common conditions, they can be difficult to diagnose. Physicians may never have seen a specific rare disease, or even be aware that it exists. In fact, an expression that is often repeated in medical schools during the training of new doctors is "when you hear hoofbeats, think horses, not zebras," a guidance to new diagnosticians that the most obvious explanations for a patient's condition are the ones best to pursue.

When research fellow Taft began working on Massimo's case, he needed to narrow down the likely suspect gene underlying the child's condition. To do so, Taft needed to sequence both of the boy's parents as a way to identify both *de novo* mutations and mutations that both parents may have contributed as a way to zero in on Massimo's pathogenic mutation. It would take about 18 months to analyze the vast amount of data in the trio of genomes, identify the genetic mutation underlying Massimo's condition, and conclude that the boy had a condition that had been previously unidentified. Today, Taft believes the work he did can be performed in a matter of weeks if not days. That's not only because of improvements in sequencing technology, but the ability today to handle and analyze large volumes of genetic data with speed. At the time, off-the-shelf solutions for doing this didn't exist. The first problem he had to solve with the trio of genomes was how to manage all of the data. Each genome was between 120 to 160 gigabytes in size. Though by today's standards it may seem like a manageable amount of data, it took Taft nearly six weeks to figure out how to store, manage, and work with all of that information.

**It will take 4.8 years from symptom onset to an accurate diagnosis of a rare disease.**

To sequence Massimo and his parents and analyze the data, Taft estimates it would have cost well in excess of $50,000 at that time. He was able to get the sequencing company Illumina to perform the work on a pro bono basis. Today, a trio of mother, father, and child can get sequenced for less than $5,000 including the analysis.

By having the parents' genomes to work with, Taft was able to narrow down the list of suspect variations to about 150 candidates. He then applied computational tools to that list to see if any of those candidates stood out. As someone trained in evolutionary biology, Taft reasoned that the variant responsible for Massimo's condition was likely in a gene that was probably highly conserved—one that has changed little through evolution and was essential since disruption to it had such dramatic effects. The gene Taft and his team zeroed in on was known as DARS. It was, in fact, an ancient gene that

# A Plan to Shorten the Diagnostic Odyssey

The Global Commission to End the Diagnostic Odyssey for Children, an alliance of more than 800 rare disease patient organizations, issued a set of recommendations to address the barriers to diagnosis for people living with a rare disease.

In 2018, the Global Commission co-chairs, Shire (now Takeda), Microsoft, and EURORDIS, formed the commission to bring together a multidisciplinary group of patient advocates, physicians, and other experts to help solve the complex challenges impacting the rare disease community.

Over the past year, the Commission gathered input from patients, families, and other expert advisors to gain key insights to guide solutions that can shorten the rare disease diagnosis timeline.

"The too-often long road to diagnosis presents one of the greatest challenges affecting the health, survival, well-being and indeed the very identity of people affected by a rare disease and their families," said Yann Le Cam, CEO of EURORDIS-Rare Diseases Europe and Global Commission co-chair. "This report identifies concrete policy and technical actions, mobilizing diverse actors to build on genetic and digital cutting-edge advances."

**The Global Commission's Year One Report's recommendations** are intended to accelerate the average five years it says it takes to diagnose a rare disease today, and to focus on distinct challenges that it says "technology is uniquely equipped to solve. "The report's recommendations fall into three broad categories that include empowering patients and their families, equipping frontline providers with tools for diagnosis, and developing ways to improve and speed access to medical geneticists for patients who likely have a rare disease.

**"Many of our recommendations address distinct challenges within rare disease that technology is uniquely equipped to solve."**

*—Simon Kos, co-chair of The Global Commission to End the Diagnostic Odyssey for Children*

In its roadmap, the Global Commission also emphasizes the importance of policies for rare diseases to be recognized as an international public health priority. The policy recommendations, designed to support the broader solution, focus on centers of excellence, genetic screening, data sharing, and privacy.

The report laid out a set of pilot programs that include multifactorial machine learning to recognize symptom patterns, collaboration tools for "intelligent triage" and clinical geneticist virtual panel consultation, and development of a secure patient registry and a rare disease passport that may use emerging technologies like blockchain.

"We believe that technology provides an unheralded opportunity to help overcome the barrier of rare, and unfortunately, 'rare' often means 'off the radar,'" said Simon Kos, chief medical officer and senior director of Microsoft Worldwide Health and Global Commission co-chair. "Many of our recommendations address distinct challenges within rare disease that technology is uniquely equipped to solve."

Taft was able to use data from yeast to help identify. Massimo had gotten one mutation for DARS from his father, and a different mutation for the gene from his mother.

The DARS gene codes for an enzyme that plays a role in the translation of RNA to the protein aspartyl-tRNA synthetase. In Massimo's case, his body produced the enzyme but nowhere to the extent it should. The condition Massimo had as a result of his genetic mutation was hypomyelination with brain stem and spinal cord involvement and leg spasticity, or HBSL for short. After identifying the gene, Taft wrote a 32-page report to arm Damiani in a search for others. He was met with incredulity by some members of Massimo's clinical team. One doctor, who today is a good friend of Taft's, sent an email calling what he'd done "science fiction."

Damiani reached out to Children's Hospital of Philadelphia and the VU University Medical Center in Amsterdam, and they were able to identify more patients. In May 2013, they published a **paper** in the *American Journal of Human Genetics* with colleagues in Australia, the United States, and the Netherlands.[7] They were quickly able to identify nine other children with the same disease as Massimo. Today, the process has accelerated. Researchers, physicians, and patients can use online systems like the **Matchmaker Exchange** that allows them to connect with others who have expressed an interest in a specific gene variant.

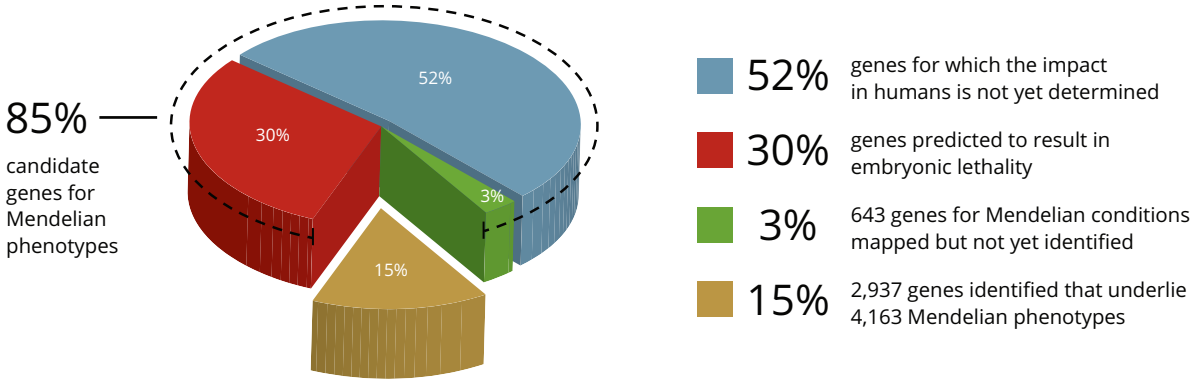
## Known unknowns

The standard of care has long relied on the clinician to form a hypothesis as to what condition a patient may have and order a test based on a patient's presentation. If the test is negative, the physician will move on to another test or a different mode of diagnostics. With genetic sequencing, physicians have the ability to test for all known genetic diseases in parallel. "We're asking clinicians, 'Is there enough here that you think any genetic disorder may underlie this patient's condition?'" said Taft. "If the answer is, 'Yes,' run a genome and then let the genome do the talking in terms of identifying changes in the DNA that look like they're not right."

Whole genome sequencing does have its limits as a diagnostic tool today. In part, that's because of the large number of variants the sequencing of any individual's genome will return and the limited understanding of pathogenic mutations driving many rare diseases. A February 2019 **study** in the journal *Genomic Medicine* [Scocchia et al.] involving a collaboration among the Illumina iHope Program, the Foundation for the Children of the Californias, and Hospital Infantil de Las Californias in Baja California, Mexico demonstrated the clinical value of whole genome sequencing on a cohort of 60 patients with a suspected genetic disease. These undiagnosed patients had indicators that included such things as birth defects, developmental delays, seizures,

**The ability to match a genetic variant to its phenotypic counterpart leaves researchers with much work to be done.**

## The Known and Unknown Connections Between Genotype and Phenotype




*Source: Chong et al., The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities, The American Journal of Human Genetics (2015), http://dx.dio.org/10.1016/j.ajhg.2015.06.009*

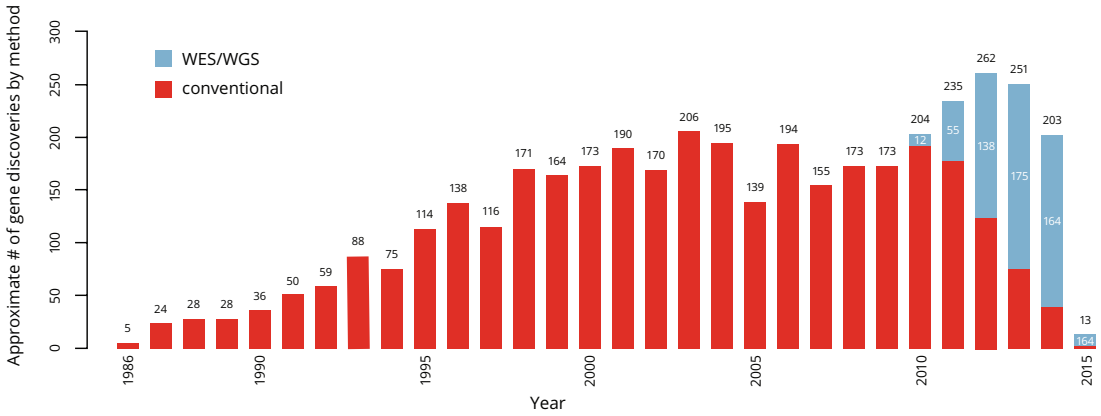
and growth restrictions. In 41 of the 60 cases (68.9 percent), whole genome sequencing produced a clinically significant genomic finding. It suggests that clinical whole genome sequencing as a first-tier test in a resource-limited environment could benefit patients with a suspected genetic disorder and avoid a protracted diagnostic odyssey through serial testing for suspected disorders.[8]

There are about 19,000 protein-coding genes in humans **[Chong et al]**. These genes make up about 1 percent of the entire genome. It is pathogenic variants of this part of the genome—the so-called coding region—that to date have been identified as the underlying cause of almost all Mendelian diseases. While sequencing today can provide about a 30 percent success rate, much of the limits have to do with the lack of understanding about how a mutation to a single gene may result in one of the estimated 7,440 rare Mendelian phenotypes identified through the Online Mendelian Inheritance in Man database (OMIN). As of February 2015, Chong et al. found that only 2,937 genes underlying 4,163 Mendelian phenotypes have been discovered. Some 3,152 of all known Mendelian phenotypes were still unknown, with about 300 new Mendelian phenotypes added to OMIN each year.[9] The ability to match a genetic variant to its phenotypic counterpart leaves researchers with much work to be done.

One reason that it may be difficult to diagnose some rare genetic diseases is because they may

## Genome Sequencing Accelerating Discovery of Pathogenic Genes

Since 2013, whole genome sequencing and whole exome sequencing have discovered nearly three times the number of genes underlying a Mendelian phenotype than conventional approaches.




*Source: The Genetic Basis for Mendelian Phenotypes: Discoveries, Challenges, and Opportunities, American Journal of Human Genetics 2015 Aug 6*

# NOT ALL GENETIC TESTING IS THE SAME

### Genotyping

Genotyping is the type of genetic testing made popular by consumer genetic testing companies like 23andMe. It will examine about 1 percent of a person's entire genome. These tests look for known variants in a list of specified genes. It will not identify a variant that is not on its list. ***Retail price $99.***

### Whole Exome Sequencing

Whole exome sequencing analyzes the portion of the genome that codes for proteins. These tests cover about 20,000 genes, but examine only about 2 percent of the entire genome. Because it looks at the genes that code for proteins, it is a powerful means for identifying pathogenic variants. ***Retail price $299.***

### Whole Genome Sequencing

Whole genome sequencing looks at virtually the entire genome. As such, it has the potential to pick up issues outside of the exome that could be involved in a genetic disease. Commercial tests are available today. ***Retail price $1,000.***

be hidden in the non-coding regions of DNA rather than in the small portion of code that provides the instructions for making proteins. Whole exome sequencing restricts itself to less than 2 percent of the entire genome and has limited capacity to detect certain types of variants. In a study from BC Children's Hospital, the University of British Columbia, an international team of researchers published a **report** in the April 11, 2019 issue of *New England Journal of Medicine* [Kuilenburg et al.] identifying for the first time a DNA mutation underlying an inherited metabolic disorder due to a mutation adjacent to the gene rather than in the gene itself.[10]

The researchers were trying to diagnose three unrelated patients. The children had early-onset delays in gross and fine motor skills, and delayed speech. All three patients developed ataxia and became dependent on a wheelchair or walker. Testing revealed that all three patients had a deficiency of the enzyme glutaminase, which is needed to convert glutamine to glutamate, an essential neurotransmitter. Though their condition is not fully understood, the researchers said it's likely that either a build-up of glutamine or the lack of glutamate caused the children's serious developmental delays and disabilities, including difficulty with language, speech, balance, and coordination. The researchers zeroed in on the gene that codes for the production of the enzyme. There was no mutation. After further investigations using exome sequencing and whole genome sequencing, the team couldn't pinpoint the error in the DNA.

Study co-authors Britt Drögemöller and Phillip Richmond discovered and confirmed that the gene responsible for the disorder was intact. Using new bioinformatic tools and a manual approach, however, they discovered a repeat expansion error in a part of the genome adjacent to the gene that prevented it from functioning. "In our search, we focused on variations that would have been hard to discover through exome sequencing," said Drögemöller, UBC postdoctoral fellow at BC Children's. "After months of experimenting with various different analyses, we finally uncovered this novel genetic variant by using new targeted approaches aimed at identifying DNA repeat expansions."

Repeat expansion disorders involve an expanding piece of genetic code that repeats over and over. Everyone has repeats in certain genes, but in some cases, people have an unusually high number of repeats that can be pathogenic. Certain rare conditions, such as myotonic dystrophy and Huntington's disease, are well known examples of repeat expansion disorders. To date, DNA repeat expansions have been linked to approximately 30 different diseases. But the researchers identified what is believed to be the first instance of a repeat expansion disorder identified in the non-coding portion of the genome. "To detect this kind of DNA multiplication, you can only use whole genome sequencing and have to search through billions of pieces of DNA; it's truly a search for the needle in the haystack," said lead author Clara van Karnebeek, associate professor in the department of pediatrics at UBC and in pediatrics and biochemical genetics at Amsterdam University Medical Centers. "With our new approach we have finally solved our mystery cases, and we now expect to find the genetic cause of other, as of yet unexplained, genetic metabolic diseases."

## Matching genotype to phenotype

Part of what's improving the ability to identify pathogenic gene variants is the proliferation of sequenced genomes as the cost of the technology has fallen. Anthony Philippakis, chief data officer of the Broad Institute of MIT and Harvard, has projected that more than 36 million rare disease patients will have their genomes sequenced by 2030, up from just 30,000 in 2017. Add in the number of relatives of patients with a rare condition who will be sequenced as part of the diagnostic process, and that number will jump to 83 million from 70,000 today. Other initiatives are rapidly expanding the number of people who have been sequenced. In fact, an **article** in the September 2018 Genetic Engineering & Biotechnology News listed at least 10 countries that had initiatives to gather, store, and use genomic data from at least 100,000 genomes.[11]

**More than 36 million rare disease patients will have their genomes sequenced by 2030.**

## Projected Growth of Sequenced Genomes by 2030

Projected figures, based on current data and known status of genomics initiatives worldwide.

| Year | Rare Disease Patients Sequenced for a Diagnosis | Rare Disease Patients and Relatives Sequenced for a Diagnosis | Cancer Patients Sequenced | Genomes Sequenced for a Cancer Diagnosis |
|---|---|---|---|---|
| 2017 | 30,000 | 70,000 | 23,000 | 50,000 |
| 2030 | 36,223,000 | 83,000,000 | 123,768,000 | 248,000,000 |

*Source: Anthony Philippakis, chief data officer, Broad Institute*

Philippakis likens the genome to a book that's been written in another language. "Back in 2000, it was a language that we understood almost nothing of, and over time we're getting better and better at being able to read this language," he said. "There are still big blocks of text that are totally unclear. There are a lot of places where we kind of know what the words mean, but we're not sure." Today, we've gotten good at being able to look at an individual's genome and identify all the positions that any given genome differs from the average genome. The challenge now, he said, is to interpret the differences that exist in any one genome and say that this change is likely to increase or decrease the risk of having this disease.

"If you think about it both for rare diseases and for common diseases, the way that we match genotype to phenotype is by getting large numbers of individuals who have the disease and large numbers of individuals who don't," said Philippakis. "That is our tool for being able to do this matching and just for reasons of statistical power we need bigger sample sizes."

Understanding the phenotype of a genetic disease can be challenging because of the rare nature of these conditions, the lack of natural histories, and the heterogeneous nature of many rare diseases. Technology is changing that in a number of ways. It is empowering patient groups to build registries and conduct natural history studies essential to allowing clinicians and researchers to understand how a given rare disease manifests itself and progresses over time. The use of imaging technology, such as MRIs, and the discovery of biomarkers related to specific rare diseases, is expanding the phenotypic hallmarks of conditions and providing researchers and diagnosticians with a more robust toolkit to match genotypes to phenotypes. One of the more powerful tools emerging in this regard is the overlaying of an individual's

## The 100,000 Genomes Club

At least 10 countries have launched initiatives to gather, store, and apply genomic data from at least 100,000 genomes.

| Country | Project | Launch Date |
|---|---|---|
| United Kingdom | 100,000 Genomes Project | 2018 (achieved) |
| Japan | Initiative on Rare and Undiagnosed Diseases | 2015 |
| China | 100,000 Genomes Project | 2017 |
| Australia | Australian Genomics Health Futures Mission | 2018 |
| Saudi Arabia | Saudi Human Genome Program | 2013 |
| United States | All of Us Research Program | 2016 |
| Estonia | Personalized Medicine Programme | 2016 |
| France | France Génomique | 2016 |
| United Arab Emirates | Dubai Genomics | 2018 |
| Turkey | Turkish Genome Project | 2018 |

*Source: Genetic Engineering & Biotechnology News, September 12, 2018*

**"There are still big blocks of text that are totally unclear. There are a lot of places where we kind of know what the words mean, but we're not sure."**

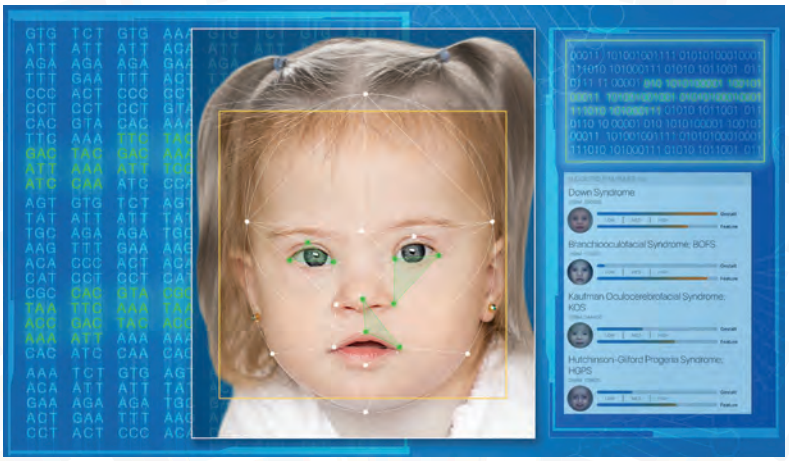
*—Anthony Philippakis, chief data officer of the Broad Institute of MIT and Harvard*

transcriptome—all the messenger RNA molecules expressed from a person's genes—as an indicator of what genes are active and to narrow down a long list of gene variant candidates and zero in on a pathogenic variant driving an individual's condition.

"Before, a lot of our information about the individual's phenotype might have been crude. There is a whole new world of collecting much richer phenotypes, whether it be molecular assays like metabolomics, proteomics, RNA sequencing, or a lot of information that can be collected through sensor devices, as well as electronic medical records, and being able to aggregate them," said Philippakis. "It's an area that we're at the very beginning of, but I see a much longer arc to it. We will have much richer phenotypic data to complement the genetic data."

New technologies are also expanding our conception of phenotype and opening the potential for new tools to accelerate the diagnostic process. Consider FDNA, a Boston-based company that is building artificial intelligence phenotyping technologies. Using images of patient faces, the company's facial recognition software is proving to be a powerful way to identify phenotypic aspects of many rare diseases. Dekel Gelbman, founding CEO of FDNA, said an estimated 2,500 to 4,000 rare diseases could be characterized by different facial characteristics. "We're helping diagnose diseases that were more difficult to diagnose without this technology because the phenotype was so subtle, barely noticeable, or maybe even so rare that doctors were not aware of it," he said. "We've actually helped people discover new diseases and define new diseases and sub-segment groups of disease that were previously considered just one type.

Critics initially told Gelbman that next-generation sequencing would render his technology redundant, but even as whole exome and whole genome sequencing technologies are being used in the clinic, the large number of variants that could be the underlying cause of a disease can be difficult to identify. The company's Face2Gene app takes advantage of the ubiquity of smartphones and cloud computing to deliver




the tool on a handheld device. "We've seen such huge advancements over the last 10 years with technology that sequences genomes. We haven't seen a single advancement beyond the capability of a physician, a human person, to phenotype a patient," said Gelbman. "We're not replacing them. We're making them kind of super physicians that are able to use technology and do much more accurate phenotyping. For the first time you're able to take a phenotype that was generated by a computer and integrate it with a genotype that was generated by a computer. This opens the door to a massive increase in the utility of genomics in healthcare."

**"We've actually helped people discover new diseases and define new diseases and sub-segment groups of disease that were previously considered just one type."**

*—Dekel Gelbman, founding CEO of FDNA*

One added benefit to using the FDNA platform is that any physician who uses it can connect to others in FDNA's network of users, including more than 70 percent of the clinical geneticists around the world. This brings a social networking dimension to the app that allows a doctor using the app to consult with others to find a diagnosis for a patient. Initially, the company relied on 130 landmarks of the face as points of measurement for its artificial intelligence system to analyze, but it has since used machine learning to allow the system to make a more refined analysis.

FDNA is also looking beyond facial recognition. It is working to layer other indicators of phenotype onto its system and is exploring such things as voice patterns, medical imaging, videos to correlate movements with a specific disease, and medical histories.

**A number of efforts are using artificial intelligence to speed diagnosis of rare disease.**

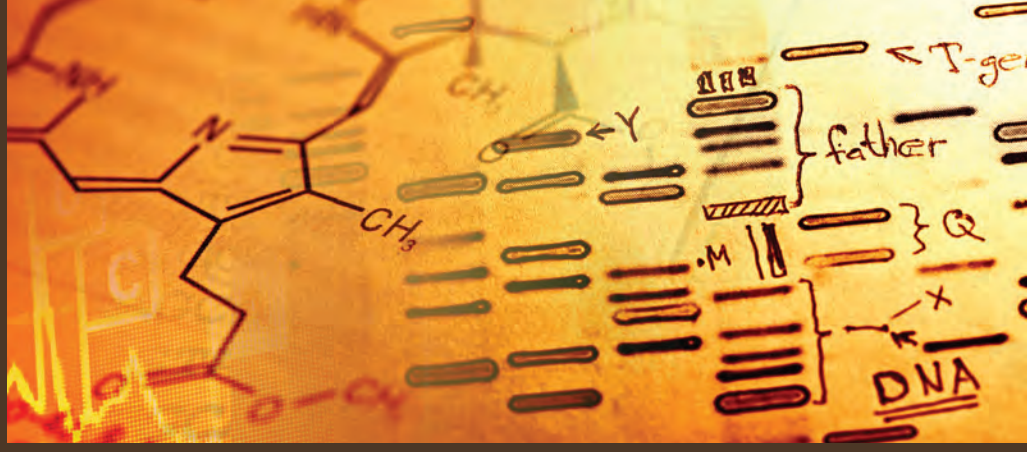
"The moment of diagnosis, understanding what your family member has, is extremely important, even if there's no treatment. It is a moment where you finally reach the end of one journey," Gelbman said. "You still have a lifetime of taking care of your family member, but at the very least, your disease has a name. You start understanding what you're facing, you start understanding diagnosis, you start understanding potentially the management of this disease. Putting a name on a disease is extremely important for the family."

There are a number of other efforts that seek to use artificial intelligence to increase the speed with which rare disease patients can be diagnosed. In a 2019 **study** published in *Science Translational Medicine* [Clark et. al], scientists at Rady Children's Institute for Genomic Medicine reported that for neonatal and pediatric intensive care patients they were able to use electronic health records and genome sequencing data to arrive at a provisional diagnosis of a rare genetic disease in a median time of less than a day.[12] The work represents the first time that rare diseases have been diagnosed using a supervised machine learning system to analyze and interpret genetic disease testing results, the investigators said.

To do so, scientists at Rady Children's Institute for Genomic Medicine used machine learning and clinical natural language processing from Clinithink, a platform that uses artificial intelligence to pull unstructured data from electronic health records to link the phenotypic information of patients with genetic results to find a diagnosis. Michelle Clark, a statistical scientist at Rady Children's Institute of Genomic Medicine and lead author of the study, created an automated pipeline to analyze the data and deliver potential diagnoses for hospitalized, often critically ill children with suspected genetic diseases. The platform automatically extracts all the clinical information that has been documented about that patient and compares the information to thousands of phenotypes and symptoms that are critical to the diagnosis of thousands of rare diseases. Because the process required minimal user intervention, investigators said they were able to increase usability and shorten the time to a diagnosis.

Other efforts seek to capitalize on machine learning to shorten the diagnostic odyssey by alerting physicians early in the process when a rare genetic disease should be suspected. One example of this is Mendelian, a United Kingdom-based company that is using artificial intelligence to build what it calls the world's largest repository of information to help accelerate the diagnosis of rare diseases.

# WHY RARE DISEASES MAY BE MORE COMMON THAN THOUGHT




Rare genetic diseases can be difficult for doctors to recognize, particularly when the symptoms of a disease fall short of dramatic, telltale manifestations described in the medical literature. While there's a tendency to think that a person either has a genetic disease or they don't, the reality may be that these diseases exist across a spectrum.

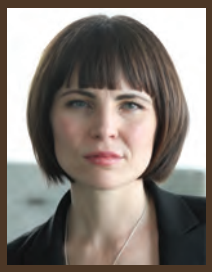
In the case of recessive genetic diseases—those that require that both parents pass the same genetic mutation to their offspring for them to develop a given condition—the ill-effects of a pathogenic version of a gene from one parent may be muted by a normal version of the same gene from the other parent. Nevertheless, it still may cause some a less severe version of a disease. Patients may also have a previously unknown variant of a pathogenic mutation that causes a milder form of a condition.

A study from researchers at Vanderbilt University Medical Center suggests people with a variety of common ailments, such as heart failure, respiratory disease, infertility, or kidney disease, may actually have an undiagnosed rare monogenic disease driving their conditions. **The study**, published in the March 16, 2018 edition of the journal *Science*, examined the electronic health records of more than 21,000 patients.[25] The researchers developed a means of scouring a set of electronic health records and assigning what they termed a "phenotypic risk score" based on the clinical manifestations of patients' conditions against the phenotypes of more than 1,200 Mendelian diseases. The researchers then examined whether patients with high phenotypic risk scores for a Mendelian disease shared any rare genetic variants associated with those conditions.

The findings were surprising. Of the 21,701 patient records the researchers analyzed, 807 patients were found to have associations between 18 genetic variants and high phenotype risk scores. Some of these variants were well known to geneticists, such as two variants that cause cystic fibrosis, but most of the associations were for variants that had not previously been identified. Of the 807 patients the researchers discovered had an underlying genetic variant to explain their symptoms, only eight had been diagnosed by their doctors to have a Mendelian disease. The rest had been misdiagnosed or never diagnosed.

The study is provocative on several levels. It not only makes the case for the importance of matching phenotype to genotype, but the approach the researchers developed to review large groups of electronic health records to score patients who may have a rare genetic condition could be used more broadly to help identify patients who are misdiagnosed or undiagnosed.

"I don't pretend to think this phenotypic score can do it on its own. It's just one more line of evidence," said Lisa Bastarache, lead data scientist with Vanderbilt's Center for Precision Medicine and lead author on the *Science* paper. She went on to say that learning more about these rare variants can help solve more undiagnosed patients and potentially allow for more tailored interventions.



**"The ultimate goal and the most exciting goal is to think about how to take this information back and impact clinical care."**

*—Lisa Bastarche, lead data scientist with Vanderbilt's Center for Precision Medicine*

"The ultimate goal and the most exciting goal is to think about how to take this information back and impact clinical care," said Bastarache. "If there are individuals that have a monogenic disease and they are not diagnosed, if knowing that information could either give them more information about their prognosis or change their treatment, that's something we want to explore."

# Using a Smartphone to Spot Rare Disease Symptoms

Credit: Juste Suminaite/KTU

**The app developed by researchers at KTU in Lithuania can evaluate a user's motor and cognitive skills to detect certain neurological conditions.**

Researchers at Kaunas University of Technology in Lithuania have created a mobile application that they say helps recognize early symptoms of **Huntington's disease**, a rare, progressive neurological disorder.

The Neural Impairment Test Suite app is a collection of various tests available to smartphone users on Google Play. The tasks on the app are designed to evaluate the user's motor and cognitive skills to detect voice and energy consumption disorders. The app can also be used for the evaluation of other neurodegenerative diseases such as Parkinson's, Alzheimer's or dementia.

Huntington's disease causes uncontrolled movements, emotional problems, and loss of cognitive ability. If a parent has the gene, a child has a one in two chance of inheriting the disease. Adult-onset Huntington's disease, the most common form of this disorder, usually appears in a person's thirties or forties. Individuals with the adult-onset form of Huntington's disease usually live about 15 to 20 years after signs and symptoms begin. A less common juvenile form of the disease begins in childhood or adolescence. It also involves movement problems and mental and emotional changes.

Early signs and symptoms of the disease can be difficult to notice. They include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. The app, designed in cooperation with physicians and the Huntington's Disease Association, provides users with a series of tests in order to check the presence of the symptoms. If the probability of symptoms is detected, the user is informed and encouraged to contact medical professionals for further advice.

"Our app is aimed at the early detection. We are attempting to diagnose the disease when visually there are no symptoms," said Andrius Lauraitis, KTU doctoral student who is developing the model for evaluating the prevalence of Huntington's disease symptoms.

Lauraitis' doctoral dissertation supervisor Rytis Maskeliunas, professor of Informatics at KTU, said the intelligent app is not intended to replace medical diagnosis.

"Due to the hereditary nature of the disease a person might know that he or she is in a risk group, but it is not known when and if the disease will strike," he said. "When the early symptoms are detected, the person is advised to contact a physician."

While there is currently no treatment for Huntington's disease, a patient can gain three to 16 years of healthy life if the disease is diagnosed early, Maskeliunas said.

Tests that are similar to the app are used in diagnostic practice today but provided on paper. This is the first attempt to digitize it. Depending on the degree of risk of developing the disease, the user can take the test once a week or more often. The individual's performance is stored in the user's profile.

The researchers said they are planning to expand the concept and the applicability of the prediction model so it could be used for other diseases.

In February 2019, the United Kingdom's Innovate UK program provided London-based Mendelian a $647,000 (£500,000) grant over two years to develop an application using its artificial intelligence platform to help general practitioners in the National Health Service identify patients who may have a rare genetic disease. In part, the system is designed to address one of the barriers patients with rare diseases face getting a diagnosis—the fact that general practitioners are trained not to consider them. The system will automatically review patient health records and alert doctors to cases where a rare genetic disease may be the underlying cause. Should the system find indicators that a patient has a rare disease, it will inform the physician and recommend specialists and tests the physician should consider. Clinicians and specialists in more than 150 countries have used its free service.

"We're not expecting doctors to think of that at first. We're trying to go the other way around by being invisible at first," said Rudy Benfredj, co-founder and CEO of Mendelian. "We'll look at the clinical records and we'll alert the doctors if there's something that warrants further investigation for that patient."

The ability of computers to review large amounts of data and compare known symptoms that correlate with thousands of rare diseases—far beyond the capacity of the training of the typical physician—is no small challenge, Benfredj admits, due to the lack of data about most rare diseases. "Usually when we talk about machine learning we have this vision that we are going to train the algorithm. We are going to give a lot of examples, ample data, and let the algorithm learn and predict," he said. "In rare disease, we have to be careful with this approach. We don't have enough sample data for a disease. We're not going to win with this approach. It's difficult to find enough of a dataset so we have to be a little cleverer."

Rudy Benfredj, co-founder and CEO of Mendelian

## Ending the diagnostic odyssey

Improvements in the accuracy and speed of sequencing technology will likely continue as the integration of phenotypic measures broadens the ability to deliver on the promise of finding speedy answers for patients. The International Rare Diseases Research Consortium, a global consortium of patient groups, industry, and academia, set as one of its ten-year goals that by 2027, any patient with a suspected rare disease will be diagnosed within a year if their disorder is known in the medical literature. Though it may seem a bit ambitious, technology is likely not to be the barrier to achieving that. The technology that exists today suggests we have the scientific ability to gather the information necessary to obtain a fast and accurate diagnosis for diseases where a genetic variant is associated with a known condition. The gaps we will need to overcome, though, involve training physicians about when to consider a genetic disease, addressing a shortage of trained genetic counselors, validating the cost-effectiveness of using new diagnostic technologies to payers, and addressing policies intended to protect patients, such as well-intended privacy protections that hinder our ability to take the data that exists today to form a better understanding of the manifestations of rare diseases to help zero-in on pathogenic genes. One of the biggest drivers of research necessary to draw the connections between genotype and phenotype have been patient organizations, which are not only funding science, but setting research agendas and changing the way it is performed. ■

**Patient organizations are one of the biggest drivers of research necessary to draw connections between genotype and phenotype.**

# A SEARCH FOR ANSWERS

**"These moms were experimenting with diet and supplements and off-label use of medications. Clearly some of the things that they were doing were working. I had a book where I was trying to keep track of the kids that I met and their developmental milestones and once I found a kid that was doing well, I would stalk their mom and figure out what that parent was doing."**

*—Maria Picone, mother of a child with Prader-Willi syndrome and founder and CEO of TREND Community*

Ellie McGinn was born in 2008. Right before her third birthday, her parents noticed she started having problems with balance. When she would go to birthday parties at a local gym, she couldn't do all of the things the other kids did, such as walking across a balance beam or climbing a ladder. Friends assured her mother Beth that she was just uncoordinated, but Beth feared the problem was more serious. She looked for answers for about nine months until a doctor, who watched Ellie walk, told Beth there was a problem with her daughter's gait and they needed to find the cause.

In the fall of 2011, an enhanced MRI revealed damage to the white matter in Ellie's brain. She was given a diagnosis of leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation, or LBSL for short. The condition, first described in 2004, is believed to affect about one in 1 million people. Though there are reasons to believe it is poorly diagnosed, there are only about 100 known cases today.

The McGinns found their way to Kennedy Krieger Institute in Baltimore, about a 45-minute drive from their home in Arlington, Virginia. Kennedy Krieger is focused on pediatric developmental disabilities and disorders of the brain, spinal cord, and musculoskeletal system. A team of physicians there began to care for Ellie. After an extensive workup, they started to treat her with a complex mixture of nutrients and amino acids to try to counter the effects of her condition. When a new study from researchers in The Netherlands suggested that LBSL would be a good candidate for a small molecule therapy, Ellie's parents became excited, but the researchers ran out of funding and didn't pursue the matter. The McGinns had started

the non-profit organization A Cure for Ellie to promote research. They had raised about $40,000 and decided to reach out to Kennedy Krieger's fundraising department to see if they had any thoughts on what they could do. The fundraising department pulled in Ali Fatemi, a pediatric neurologist who has since become chief medical officer of the institute. It began a discussion that today has led to an ongoing effort to find a treatment for the condition.

In April 2018, Kennedy Krieger initiated a natural history study of LBSL. Little is known about the condition and the researchers are trying to determine such things as how the disease progresses, how much variation is seen from patient to patient, whether there is cognitive involvement, and how different variants of the DARS2 gene—the gene responsible for driving the condition—correlate with the severity of the disease. To address the challenge of conducting a study on a geographically dispersed group of patients over a few years, Kennedy Krieger hit upon an innovative solution. Rather than bring patients to Baltimore, Maryland every six months to track changes in their condition, it would outfit participants with technology that could allow the researchers to test patients remotely. In addition to providing insight into the condition, the data being gathered may also be used as a historical control for a future drug trial should researchers identify a therapeutic candidate. Ellie was the first patient enrolled in the study.

Using devices that are similar in appearance to consumer fitness wearables like the Fitbit, Ellie places bands on her ankles, wrists, and waist.

The McGinn family

The devices are able to measure movement in space, acceleration, and deceleration. They send data to a nearby receiver that is also provided to the patient. A researcher connects through a video call with a camera and computer supplied to the patient and guides them through a series of tests.

"These people are scattered all over the world. They don't have the means to travel and we don't have the means to pay for their travel. We are supporting research on a shoestring budget," said Beth McGinn. "Even those that could travel, and have the means to pay their own way, may feel the physical toll it takes is simply not worth it for them. Some of these kids are really delicate."

At a time when competition for traditional sources of research funding continues to intensify, particularly for younger investigators, rare diseases advocates have discovered the

Ellie McGinn, who has LBSL, uses remote monitoring devices as part of a study

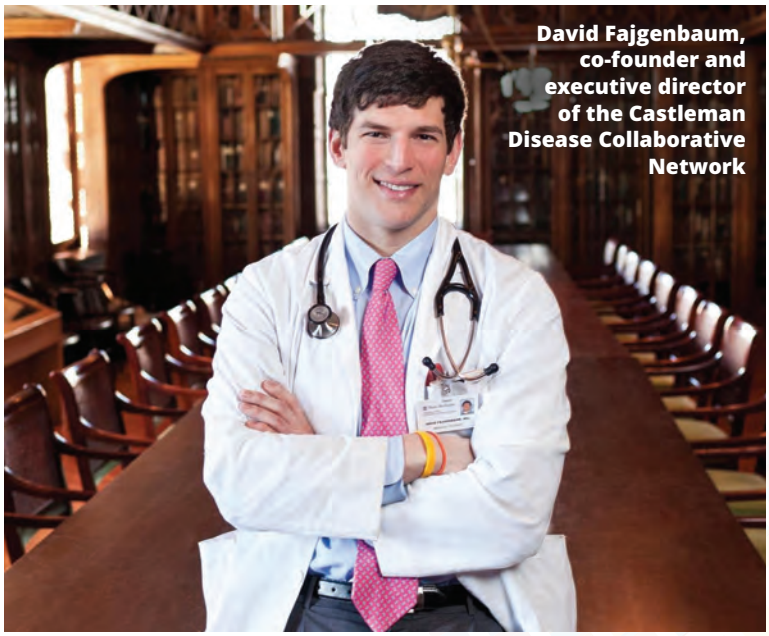
**"I gave up on getting researchers to share samples. The main way we push forward science is by getting them directly from patients."**

*—David Fajgenbaum, co-founder and executive director of the Castleman Disease Collaborative Network*

power they can have in attracting the interest of researchers. By providing funding, they are driving foundational and translational research to understand the mechanism and progress of a given disease, identify biomarkers, and advance potential therapies toward the market. They are becoming more sophisticated about how to shape a research agenda, put into place new approaches to accelerate the process, and address barriers to progress in rare diseases research. In so doing, they are also harnessing technology to change the way data is collected and shared.

## Collaboration is critical

David Fajgenbaum became stricken by a mystery illness when he was a third-year medical school student. He soon suffered multiple organ failure and was placed in the intensive care unit. His condition grew so dire that his parents were told to say their goodbyes and a priest read him his last rites. By then, doctors had diagnosed him as having idiopathic multicentric Castleman disease, part of a group of rare and poorly understood hematologic disorders where the immune system turns on the body. Fajgenbaum's subtype is the deadliest and characterized by episodes of intense inflammation and multiple organ system dysfunction.

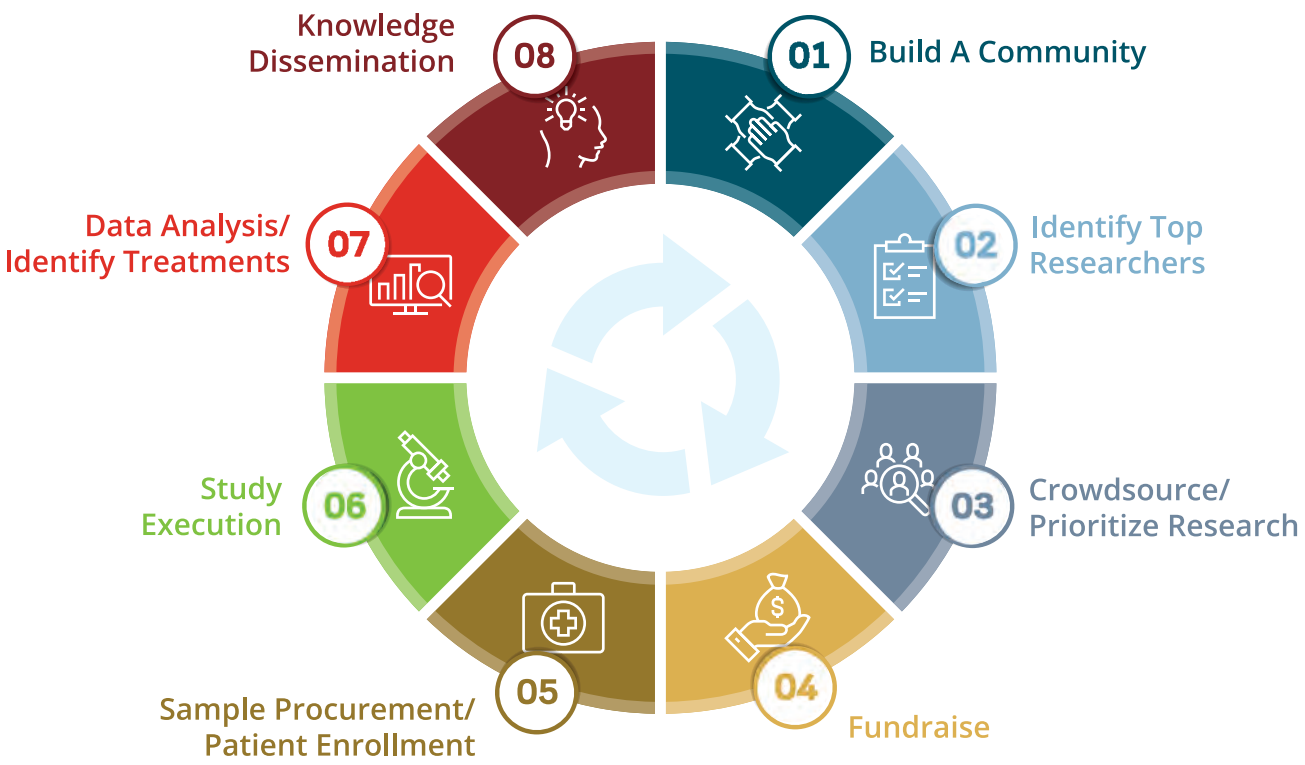


**David Fajgenbaum, co-founder and executive director of the Castleman Disease Collaborative Network**

In a last-ditch effort to save Fajgenbaum, doctors administered an off-label therapy that saved his life. When he left the hospital more than four months after being admitted, he left the work of Castleman disease research in the hands of others and continued down the path to becoming an oncologist. But when he relapsed 15 months later, he took a much deeper dive into the world of Castleman disease research. He discovered that while researchers around the world were studying the condition, none were working together. They were each using different terminology and classification systems, and none of them seemed to understand how the work they were doing related to the research others were conducting.

In August 2012, Fajgenbaum launched the Castleman Disease Collaborative Network (CDCN) with the hope of improving collaboration, developing a global research strategy, and driving research forward in the most cost-effective and efficient manner. One of the things he was worried about, as he looked at the range of research being performed on Castleman disease, was that there were only a handful of researchers studying the disease and they didn't represent the full breadth of the types of research that could be done. "I was concerned that if we raised money and asked people to fight for it, there

**The Eight Steps of the CDCN's Collaborative Network Approach**




was a likelihood that the best researchers for the kind of work that needs to be done wouldn't actually apply to do the work," he said. He wanted to turn that process on its head by having the community identify the research agenda and then find the best scientists to carry it out.

In an April 2019 **review article** in the journal *Emerging Topics in Life Sciences*, Fajgenbaum, along with his organization's COO Mary Zuccato, and Senior Scientific Advisor Dustin Shilling, laid out their organization's approach to research. In so doing, they provided a roadmap for other rare disease organizations wanting to avoid the pitfalls traditional approaches to research pose for rare diseases.

The traditional research model involves groups raising money, inviting investigators to apply for funds to use how they see fit, and a group of advisors choosing who should get those funds. The authors say this approach works well in disease areas where there is a competitive landscape and research materials are abundant. But in rare diseases where there are limited qualified researchers interested in working on a specific disease, the chances that a highly qualified researcher will pose a high-impact research project becomes much more unlikely.

Instead, the approach CDCN established involves identifying the stakeholder community, having the community prioritize a research agenda, and recruiting experts to conduct the studies. Building on the work of a number of rare disease organizations, the authors describe an eight-step approach. The process also involves raising money for the studies that need to be conducted, recruiting patients and patient samples, and assisting with the execution of studies by providing project management and scientific advice. The two final steps involve data analysis with a focus on identifying a potential treatment (particularly already approved therapies that could be repurposed), and disseminating the information by helping publish and distribute the findings.

"This final step ensures that the community, described in Step 1, is well informed about scientific progress and therefore better able to identify and prioritize the next round of high-impact research," the authors write. "After disseminating findings throughout the community, the cycle continues: more individuals join, new research ideas are shared (inspired by the findings), and greater progress towards the CDCN's mission is accomplished."

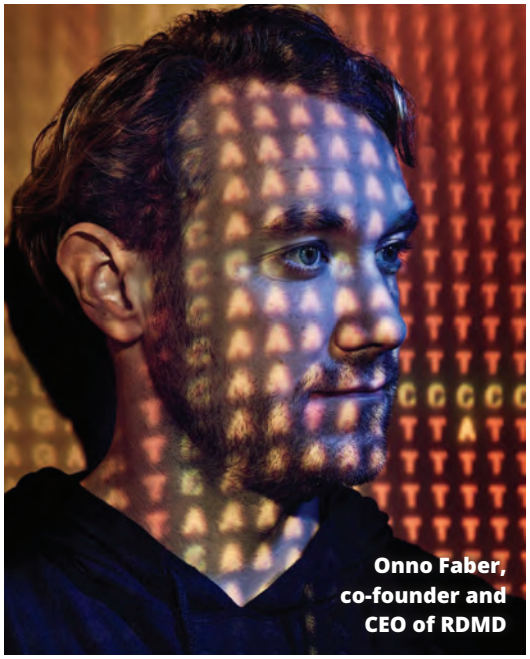
The effort has required finding novel solutions as they arise. One unexpected challenge Fajgenbaum found was the difficulty of getting physicians and researchers to share blood and tissue samples. "That's been a lot harder than I anticipated. I gave up on getting researchers to share samples," he said. "The main way we push forward science is by getting them directly from patients. We process the samples, then we make them available to researchers who want them."

Prior to the CDCN's founding, there were few advances in the understanding or treatment of Castleman disease. There was no foundation focused on advancing research, limited collaboration between researchers, no centralized registries or biobanks, and few published studies. What studies existed had limited sample sizes, inconsistent terminology for subtypes of the disease, and different approaches to stratification that made comparisons between studies difficult. The combined effect of this was to slow the understanding of the disease and the identification of potential targets and therapies.

The CDCN's approach has changed the landscape for Castleman disease. It has made significant progress toward the goal of finding therapies for all types of Castleman disease. Since its founding in 2012, the CDCN has connected and engaged more than 500 physicians and researchers and more than 10,000 patients and family members. With these communities it has developed and carried out an international research agenda that has supported 23 research projects with samples, study coordination, and/or data analysis. It has also funded 19 projects and facilitated the publication of more than 20 research papers, including a uniform Castleman disease classification system, and multiple case series describing more than 400 patients. It has developed the first-ever diagnostic criteria for idiopathic multicentric Castleman disease and the first-ever treatment guidelines for this form of the disease. CDCN members also served as investigators on the clinical trials that led to the first-ever FDA-approved therapy for idiopathic multicentric Castleman disease.

## Breaking down silos

One fundamental challenge researchers face in studying many rare diseases is getting access to enough patient data. Because of the rarity of a condition, patients can be difficult to find. And data can often become siloed because of its perceived commercial value, privacy concerns, limits of existing informed consent agreements, or the desire of individual researchers to control data for their own career benefit. Onno Faber recognized that problem when he began searching for a treatment for his own rare condition, neurofibromatosis 2 (NF2), a genetic condition that involves the growth of noncancerous tumors on the nerves that carry signals between the inner ear and the brain and can affect hearing and balance.



**Onno Faber, co-founder and CEO of RDMD**

Faber, a tech entrepreneur who had moved from the Netherlands to the San Francisco Bay Area, was diagnosed after he began losing his hearing. After having his genome sequenced, he worked with Silicon Valley AI, a community of scientists and researchers with backgrounds in artificial intelligence, machine learning, and biology, to organize a hackathon. Google provided $150,000 worth of cloud computing power to support the weekend effort, which attracted about 300 computer and life scientists (including neurofibromatosis experts). Multidisciplinary teams worked to see what they could make of Faber's genetic data. By analyzing Faber's tumor DNA and comparing it to the DNA from other tumor types they identified approved drugs that might be repurposed to treat his condition. Others at the event identified potential new compounds that could treat Faber's NF2, while others identified new mutations.

One problem apparent to Faber through the process was that the assembled hackers didn't have access to the DNA of other patients with his condition. Faber tried to obtain other patient data for the hackathon but was stymied by regulatory, legal, and other constraints that left it inaccessible even though he knew it was out there. "I thought that would be really cool if patients who had their own data could find a way to put it all together and create bigger sources of information for research," said Faber, who founded RDMD, a company seeking to aggregate rare patient health data. "That's how I got started with RDMD—to give patients the opportunity to take their data and provide it directly to researchers and drug developers."

RDMD is creating a platform through which patients can control and share their health information. By making available patient data in medical records that today are often inaccessible to researchers and drug developers, RDMD seeks to accelerate the drug discovery and development process. Faber describes the platform as "patient-driven." It takes about 10 minutes for someone to sign up and then they are done. RDMD collects all of their medical records and creates de-identified research data sets. RDMD is providing the data free of charge to academic research sites with which it works. Patients, though, own their data and can access it through RDMD, or share it with a doctor. Ultimately, RDMD's business model is to charge drug developers for access.

RDMD is not alone in seeking to build a technology platform that can aggregate patient data while allowing patients to control who has access to it. Nebula Genomics and LunaDNA are two companies offering patients an opportunity to not only drive research but also have an economic stake in how their health and genomic data are used. How patients share in the economic rewards varies under the different approaches of these two companies. In the case of Nebula, the enticement is that it allows people to offset the cost of having their genome sequenced through credits they can earn by sharing their information.

"We're trying to set things up in a way where people can feel more involved, where they know who they're giving the data to, they know what purpose it will be used for, and possibly even receive some feedback later saying, 'The study led to this and that,'" said Dennis Grishin, co-founder of Nebula. "That's how we think it should work and that's what we think will encourage many more people to participate."

Nebula is using blockchain, a technology created to track cryptocurrency transactions. It turns out that blockchain is a good fit for addressing the problem Nebula sought to solve by providing a secure and encrypted way to decentralize the storage of the data while allowing individuals to control and trace the use of their personal information.

Grishin and Kamal Obbad were graduate students at Harvard when geneticist George Church reached out to them to help figure out how he might improve on the Personal Genome Project, a nonprofit he started in 2005 to collect and share genomic and health data. The Personal Genome Project is a repository of genetic and health data with the individual's consent for research use. It was built on an open-access model and is one approach to address the problem of siloed data.

**By putting the registry online, participation is possible for a geographically diverse group of patients and caregivers.**

**"If we decide we want our patient registry to do something and we engage developers to do that, then everyone else using the platform has those features available."**

*—Megan Cross, chairperson of the Foundation for Angelman Syndrome Therapeutics*

"It's a gigantic concern, it's been one of the things I've been concerned about since roughly 2005, when I started the Personal Genome Project. The Personal Genome Project is one extreme solution to that problem, where you just make sure people are educated and have consented to open access," said Church. "Most people are not comfortable with that. It's a great resource for the subset who are willing to do it. We need a solution that works for everybody, and we think that that requires homomorphic encryption and blockchain to get that to go."

## Common problems, shared solutions

One of the starting points for rare disease patient groups that seek to advance research in a specific condition is the creation of a patient registry and natural history study. Traditionally these types of studies are conducted in hospitals. The Foundation for Angelman Syndrome Therapeutics Australia has developed a caregiver-initiated research project. The organization is collecting natural history data through a series of online modules that cover all the facets of the syndrome. By putting it online, participation is possible for a geographically diverse group of patients and caregivers. To further expand the reach of the registry, the organization is translating it into multiple languages including Mandarin, Italian, Spanish, Portuguese, and French. Megan Cross, chairperson of the Foundation for Angelman Syndrome Therapeutics Australia said most of the previous registries have been in the United States and they are missing large swaths of the patient population and possibly not capturing the full diversity of the condition or the range of issues patients and caregivers face.

Cross, who has a background in information technology, said she understood what data collection looked like and how powerful it could be. When her daughter Molly was diagnosed with Angelman syndrome, a rare neurodevelopmental disease, she wanted to approach the syndrome analytically and searched for information. She was surprised she couldn't get a hold of a bulk of information to answer questions she had. She looked at off-the-shelf solutions for gathering such data and spoke to other rare disease organizations when she came across the work of the Centre for Comparative Genomics at Murdoch University in Perth, Australia.

The Foundation for Angelman Syndrome Therapeutics Australia created The Global AS registry, a web-based, global, patient-driven registry. Launched in 2016, the registry now includes about 1,000 patients. The registry is expected to help medical professionals and researchers better understand the condition and provide a means for drug developers to identify participants for clinical trials. It is built upon the Rare Disease Registry Framework, an open-source framework developed by the Centre for Comparative Genomics. The modules guide users through a series of questionnaires. Modules include such things as newborn and infancy history, history of diagnosis and results, illnesses or medical problems, medical history, behavior and development, epilepsy, medications and interventions, sleep, and more. Longitudinal data is collected annually.

The Rare Disease Registry Framework allows anyone who wants to create a patient registry to do so without being a programmer or having knowledge of coding. Because it is an open-source platform, it provides the

economic benefits for everyone to capitalize on improvements anyone makes to the software. "When someone else invests in functionality, then it's available to everyone else," said Cross. "If we decide we want our patient registry to do something and we engage developers to do that, then everyone else using the platform has those features available. Of course, that means we can share development and team up to get things in a more cost-effective manner."

## Patient-reported outcomes

The ability to capture patient and caregiver input in new ways is helping change research and drug development into a more patient-centric approach where drug companies and regulators consider what outcomes are most meaningful to patients. The use of technology to drive this is also placing greater power in the hands of patients to identify potential therapeutic benefits of such things as repurposed drugs without engaging the academic-pharmaceutical industry collaboration, which can be both costly and difficult to set into motion.

Consider Lara Pullen, whose son was diagnosed with Prader-Willi syndrome, the most common genetic syndrome causing morbid obesity in children. Pullen, who is co-founder of the Chion Foundation, has a doctorate in microbiology/immunology. She dove into the scientific literature around Prader-Willi after her son was diagnosed with the condition. Endocrinologists primarily treat the disease because it is often associated with intense appetite, diabetes, and obesity. But it is a complex condition that involves muscle weakness, developmental and intellectual disability, sleep apnea, and daytime sleepiness. As Pullen read studies that had been conducted on Prader-Willi syndrome, she decided that she would focus on the data, rather than the conclusions and see if that led her in any new directions.

"I tried to pull the threads of the data and see where they took me," she said. "A lot of them, to me, looked like the entire system of a child with PWS was off, that it was not just an obesity phenomenon, but that the system of homeostasis in the body was off."

**Kian and Lara Pullen**

**"I was struck by what seemed to be a huge gap between what was written in the literature and what was actually possible for a child born today with Prader-Willi syndrome."**

*—Maria Picone, co-founder and CEO of TREND Community*

Though Pullen's doctorate degree is in immunology, her thesis work sat at the intersection between the immune system and the nervous system. She was accustomed to thinking about problems from that perspective, and how the different systems interact. As she dug deeper into the research, everything kept pointing Pullen back toward the nervous system. One thing that caught her attention was that the histamine 3 receptor, which is found in the brain, plays a role in regulating sleep and wake states, hunger, alertness, anxiety, and REM sleep. The more she read, the more she was taken by how the histamine 3 receptor aligns with different problems in Prader-Willi patients. "I was shocked at how well the two things lined up," she said. "The overlay was unbelievable. I could use it to account for all the different pieces of data that couldn't really be explained by this whole of PWS being primarily about obesity."

Based on patient- and caregiver-reported symptoms, Pullen argued that Prader-Willi syndrome often aligns with symptoms of narcolepsy with cataplexy, a rare condition involving daytime sleepiness and sleep apnea. It so happened that in 2016, the European Medicines Agency approved pitolisant, a treatment for narcolepsy that targets the histamine 3 receptor. Pullen reasoned the drug might benefit patients with Prader-Willi.

Pullen obtained a prescription for the drug from her son's physician, purchased it in Germany, and imported it to the United States under a personal importation route allowed at the FDA's discretion. She enlisted other families to do so as well. The families agreed to document their experience using the TREND Community platform, which allowed caregivers to track and report on their experiences using pitolisant. In a **clinical vignette** in the March-April 2019 issue of the *Journal of Pediatric Pharmacology and Therapeutics* [Pullen et al.], researchers reported that pediatric patients with Prader-Willi who used pitolisant had decreased daytime sleepiness and improved cognition. They argued that the drug may represent a novel therapeutic option that might relieve substantial disease burden associated with the condition.[14] Harmony Biosciences, developer of pitolisant, is expected to pursue a clinical trial in Prader-Willi syndrome.

Maria Picone, co-founder and CEO of TREND Community, had a background in digital health when her daughter was born with Prader-Willi syndrome. When doctors delivered the diagnosis, they gave Picone and her husband a sheet of paper that described what to expect and what her life would be like. Picone began to dig through the medical literature to understand what Prader-Willi syndrome was, and what it meant for their daughter and family. Picone made her way to a private Facebook group for caregivers of children with Prader-Willi syndrome.

"Having worked in digital health and clinical trials and all of that for so long, I was struck by what seemed to be a huge gap between what was written in the literature and what was actually possible for a child born today with Prader-Willi syndrome," Picone said. "These moms were experimenting with diet and supplements and off-label use of medications. Clearly some of the things that they were doing were working. I had a book where I was trying to keep track of the kids that I met and their developmental milestones and once I found a kid that was doing well, I would stalk their mom and figure out what that parent was doing."

The first generation of TREND relied on using conventional methods, such as surveys and traditional data collection to systematically gather anecdotes and then to try to make sense of them to figure out what was working. "We've found that those traditional methods—registries, clinical trials, natural history studies—are really important but they're very difficult to maintain for someone whose life is already very difficult, and time is a commodity. It's hard to keep up with all of those things and keep them current," she said. "But patients and caregivers are sharing all of the details about their lived experiences on social media in these private groups, especially ones that are focused on specific rare diseases."

In 2017, TREND Community began to focus on developing analytics to apply to unstructured data sources, such as private Facebook groups, email, Twitter, Reddit, as well as disease-specific platforms like Inspire or PatientsLikeMe. The company, with the permission of these groups, pulls out conversations and runs analytics on what is there. TREND is part of a broader effort within the rare disease community to gather patient experience data in response to the FDA's Patient-Focused Drug Development Initiative, which was expanded in 2016 through the 21st Century Cures Act, signed into law in 2016. The TREND Community allows parents to document and quantify real-world data in a manner that can be used to inform the FDA and the medical community of patient experience.

Its first project using its ability to analyze unstructured data involved analyzing the Friedreich's Ataxia Facebook group for the Friedreich's Ataxia Research Alliance ahead of an externally-led patient-focused drug development meeting with the FDA. In preparation for that, the patient organization had sent out a survey to 1,000 members of their community but only received 200 responses. The group turned to TREND to see if its analytics could help establish insights into the disease burden, disease management, quality of life, and unmet needs within the community, which it did.

## Converging disciplines

As biological research increasingly becomes a data science, it is changing the nature of research. Information technology is enabling individuals to access stores of data to gain new insights through analysis of existing data and the overlay of genetic data and health records. As more and more data become accessible, individuals are able to find connections between not just phenotype and genotype, but between various medical conditions and a given rare disease. By doing so, it may be possible to identify common biological mechanisms and use that to identify drugs effective at treating one condition that may serve as therapeutic alternatives to treat other conditions that are without treatments.

Consider Matt Might, the parent of Bertrand Might, the first patient diagnosed with the ultra-rare condition NGLY1 deficiency. Today, Might is the director of the Hugh Kaul Precision Medicine Institute at the University of Alabama at Birmingham. Might is a computer scientist, not a biologist, by training. For Might, precision medicine is fundamentally data-driven medicine. "When you incorporate all the data you have about a patient, which these days may include their genome, you end up creating very tailored treatments for a specific patient. Because you can get very tailored treatments, it has a natural pull," he said. "We're all going to want to move in that direction because no one wants one-size-fits-all care. That's especially true for rare diseases where you really do need that very individualized, very tailored treatment."

**For Might, precision medicine is fundamentally data-driven medicine.**

Bertrand had been developmentally stuck at around nine months for a long time, according to Might. He was at serious risk of losing his vision and now his vision is perfect. He's gone from having hundreds of seizures per day down to none. He still struggles with his movement disorder, but he is making progress in terms of his communication. He can use an eye-gaze computer that tracks his eye movement to operate it rather than a mouse. He can express his intent, and he's

even asked for a pet fish. All of that, said Might, is not something he could have done three years ago.

There are three treatments that have changed Bertrand's condition. The first came when Bertrand was seven years old. Bertrand suffered from a lack of tear production, which was causing corneal damage and slowly destroying his eyesight. Might discovered that N-acetylglucosamine, a natural product found in the shell of shellfish could benefit his son. Might is not sure about the biological mechanism, but when N-acetylglucosamine, a simple sugar, was tested in fly models of NGLY1-deficiency, there was a dramatic increase in the survival rate of flies from the larval stage of

Bertrand and Matt Might

development, rising to 80 to 90 percent from just 7 to 8 percent. When he started using it, it helped his tear production and vision.

The next treatment came when Bertrand was nine. By doing a computational search, Might discovered that Prevacid, a proton-pump inhibitor used to treat acid reflux, happened to be the right shape to hit a target in the brain that could address Bertrand's frequent seizures. After trying the drug in a worm model of the disease, he administered the drug to Bertrand. Although he can't definitively attribute the improvements to Prevacid, he said use of the drug correlated with an end to Bertrand's seizures.

Using artificial intelligence, Might identified a connection between the NGLY1 gene and a gene called NRF1. It turns out that NGLY1 deactivates NRF1. He also found that increasing the activity of the NRF2 gene could compensate for the absence of NRF1. Sulforaphane, a compound abundant in broccoli and available as a supplement, increases the activity of NRF2. When Bertrand was 10, he began taking sulforaphane supplements, which appear to have improved his cognitive abilities.

Might is working to enable other rare disease patients in need of therapeutic options to benefit from the approach he's taken with his son. The Precision Medicine Center where Might works has been developing a tool called mediKanren, an artificial intelligence agent that reads natural language and has reviewed published medical studies and abstracts for some 29 million papers. It has boiled down all of that information to data, such as X inhibits Y, or W treats Z.

The center will run the searches for patients, but it is not a clinical center. If it makes what it believes is a relevant finding, it will engage with a patient's physician and share the information in a research report. The physician will then make the decision whether or not to act on that information and share it with the patient. Might said already between 5 percent and 8 percent of the patients who turn to the Precision Medicine Center will come away with a treatment recommendation for their physician to review.

Separately, Might wants to help individual rare disease patients find potential treatments by repurposing existing therapies. He co-founded the company Pairnomix, which in 2018 merged with Q-State Biosciences, an integrated precision medicine drug discovery company. For patients with a rare genetic epilepsy, the company will conduct a screen to see if it can identify any drugs that could potentially act on the patient's specific mutation. The company creates a laboratory model of the patient's

**"By building models of a patient's exact disease, it enables us to develop targeted therapies that shorten the time and cost to treating a patient."**

*—Matthew Fox, CEO of Q-State Biosciences*

genetic mutation and screens more than 2,500 approved drugs against the model and its functional consequences. The company also has a library of new chemical entities it can use to screen against a target. The findings are provided to the patient's physician, who can then consider them.

Separately, Q-State Biosciences is working with leaders in antisense oligonucleotide (ASO) technology to design ASOs in a research setting that can prevent the production of pathogenic proteins or rescue expression of a protein that produces a beneficial effect. ASOs are synthetic fragments of DNA that can bind to messenger RNA and disrupt the disease process of a patient with a pathogenic genetic mutation. This class of therapies represents a promising modality for treating a range of rare genetic diseases and has already become available commercially. Spinraza, Biogen and Ionis' treatment for spinal muscular atrophy type 1, is one such example. "This approach will address the root cause of genetic disease," said Matthew Fox, CEO of Q-State Biosciences. "By building models of a patient's exact disease, it enables us to develop targeted therapies that shorten the time and cost to treating a patient."

Q-State provides ASO research services for select genetic mutations implicated in certain neurologic disorders and tests ASO candidates in disease-relevant cellular assays. The findings are then delivered to the patient's physician. The company said it plans to engage the FDA for help in navigating the regulatory processes required to provide a clinical ASO option for patients who may be good candidates for this approach, suggesting the potential for custom-developed therapies to treat rare disease patients.

Such an approach has had a proof-of-concept. In October 2018, ***STAT*** reported on how Timothy Yu, a neurologist and physician scientist at Boston Children's Hospital had been able to rapidly conceive and deliver an ASO therapy for a 6-year-old girl with the ultra-rare CLN7 form of Batten disease, a deadly neurodegenerative disease.[15] Yu led the effort that involved dozens of scientists to conduct necessary testing and manufacturing, as well as navigate the FDA's compassionate use, or expanded access, procedures. The treatment appears to have halted the progression of the disease. While the case was held out as unusual, it does suggest Q-State and others might be able to systematize such an approach for patients without therapeutic options for diseases where the economics of traditional drug development may be too daunting a barrier to engage a drug company. It suggests some of the dramatic changes that are reshaping the development of therapeutics as well, which increasingly rely on N-of-1 approaches, the power of artificial intelligence to accelerate development, the use of repurposing as a faster and cheaper way to get to much needed treatments, and the use of new therapeutic modalities to act on the root molecular cause of a disease. ■

# THE SEARCH FOR TREATMENTS AND CURES

**"When you're dealing with a network of tens of thousands of genes, hundreds of thousands of proteins, and trillions of interactions every second in every cell in our body between these proteins, that's not something we're going to be able to solve with the capabilities of the human brain. AI has this pretty incredible ability to synthesize vast quantities of data that are much too big for any human, or any collection of humans, to work through, understand, and to see patterns in that scale of data."**

*—Chris Gibson, co-founder and CEO of Recursion Pharmaceuticals*

It was during a chance meeting at the UK Genetics Disorder Symposium in London when a representative of the U.K. affiliate of the Barth Syndrome Foundation began a conversation with Tim Guilliams, a tech entrepreneur and CEO of Healx, a startup that was using an artificial intelligence platform to identify drugs that could be repurposed to treat rare diseases. Proponents of repurposing see this approach as the fastest and most cost-effective way to bring treatments to market for the vast majority of rare diseases that today remain without an approved therapy. The benefit of this approach is that there are a wide number of compounds that are well characterized and have gone through clinical testing to establish their safety. By scouring these compounds to find ones that may have activity in a given rare disease, they can follow an abbreviated path to approval and be made available to patients at less cost than a novel compound developed for a small population of patients.

Healx co-founder and chief scientific officer David Brown is a 40-year veteran of the biopharmaceutical industry and perhaps best known as a co-inventor of Viagra, a drug that had been discovered as a possible treatment to lower blood pressure and treat angina. Viagra became a blockbuster as the "little blue pill" for male sexual dysfunction and a poster child for repurposing as it

**"We need to drive R&D and attract interest in our rare disease. We can't hope that people are going to be looking on the Internet and say, 'Oh, I should just apply to them for a grant.' "**

*—Emily Milligan, executive director of Barth Syndrome Foundation*

demonstrated that a compound developed for one purpose could have benefits for other conditions. "The traditional pharma model is broken and is not viable for rare diseases. AI has the potential to revolutionize drug discovery," said Brown on the company's website. "Using our technology platform, we have shown that we can translate drugs into the clinic 80 percent faster and about 90 percent cheaper than traditional drug discovery."

The discussion that began in London with the Barth Syndrome Foundation turned into a full-fledged collaboration in 2019 to use the Healx artificial intelligence platform to repurpose potential drugs to treat Barth syndrome, a rare genetic disease characterized by skeletal and cardiac muscle weakness, and potentially fatal arrhythmias. How and when the condition manifests varies greatly, but many children with the condition die of heart failure or infection. Those who survive childhood can live into adulthood and reach their late forties. The agreement with Healx reflects a growing trend in the rare disease space for an advocacy organization to move beyond driving basic research to take an active role in driving drug discovery and development rather than waiting for traditional biopharmaceutical companies to become involved.

"We need to drive R&D and attract interest in our rare disease. We can't hope that people are going to be looking on the Internet and say, 'Oh, I should just apply to them for a grant.' It is incumbent on us to go out and drive that. We have to be out there beating the bushes,"

**Tim Guilliams and David Brown, co-founders of Healx**

**"What you do is you predict drugs that will compensate and restore your disease profile to a healthy profile. That's much more sophisticated than 'Here's your one gene mutation or target.' You actually look at 22,000 genes."**

*—Tim Guilliams, co-founder and CEO of Healx*

said Emily Milligan, executive director of the Barth Syndrome Foundation. "Part of that will be the more traditional R&D pathway—discovery, preclinical, and then going into clinical studies—but we want to be open to alternative methods as well, like the AI work we are doing right now."

Healx's HealNet platform scours scientific literature, discoveries, publications, clinical trials information, and other sources to predict existing treatments that may be safe and effective for treating a specific rare disease. It is using knowledge graph technology, the basic technology Google uses for its search algorithms, to mine the top treatment opportunities in the same way a Google search will rank the most relevant responses to a query. Healx believes it's built the most comprehensive rare disease knowledge graph that there is today with more than a billion relationships. The hope is to use known discoveries and relationships to find new discoveries and relationships.

For any disease it pursues, there is a set of biological data Healx likes to have. It works with the patient groups with which it partners to inventory that data and have them fill in the gaps with their academic partners to the extent that is possible. This may include such things as producing gene expression, and proteomic and metabolomic data relating to a specific condition. Though a condition like Barth syndrome may be driven by a mutation in a single gene, Guilliams said what investigators want to understand is the disease biology and the way the entire network of genes and proteins may be disrupted as a consequence of the mutation that drives the condition. By looking at the entire genome and the transcriptome—the collective messenger RNAs of a patient—and comparing healthy patients to patients who have a specific disease state, a picture of the pathways and genes that are being dysregulated can emerge. "What you do is you predict drugs that will compensate and restore your disease profile to a healthy profile. That's much more sophisticated than 'here's your one gene mutation or target'; you actually look at the 22,000 genes," said Guilliams. "That helps predict existing treatments or treatments that are safe for that rare disease. That's really the quickest and the cheapest way of finding a potential treatment."

In the case of Barth syndrome, Healx is taking its predictions and then testing them with induced pluripotent stem-cell-derived cardiomyocyte models of Barth syndrome developed by Boston Children's Hospital cardiologist William Pu. By testing compounds in these cells and then analyzing the messenger RNA, researchers could get a fast indication of a compound's potential efficacy. It's a model that Pu believes could be used across rare diseases.

The Barth Syndrome Foundation is not alone in working with Healx. Another collaboration involves FRAXA Research Foundation, which is working to find treatments for fragile X syndrome, a rare genetic disease associated with developmental delays, intellectual disabilities, and behavioral issues. The two began collaborating in September 2016. Within six months, Healx had identified eight lead drug candidates. Though FRAXA had been exploring a number of potential drugs to repurpose as treatments for fragile X, the compounds Healx identified had not been previously linked to fragile X syndrome. In addition, the project identified new potential targets involved in the disease. FRAXA's

Drug Validation Initiative tested three prime candidates. All had beneficial effects on fragile X behaviors in mice. The most promising candidate, which showed positive results in all four behavioral assays tested, was chosen to progress to a phase 2a clinical trial and did so in a matter of 19 months from the initiation of the work. The second leg of the collaboration is continuing as Healx found that combinations of the drugs it identified might have the most significant benefits for fragile X patients. FRAXA said it believes that intelligent combinations of drugs will be required to obtain clinically meaningful responses in a wide range of fragile X patients, as well as other rare diseases.

"It's going to be a massive, positive disruption. You can already apply our technology at scale and in a massively parallel way. We plan to possibly take 100 rare disease treatments to the clinic, which is a scale that a small company couldn't do with a staff that's now about 35," said Guilliams. "There will be a very low-cost way of identifying potential drug candidates. Then adaptive clinical trials will allow you to start testing those on very small populations in a way [where] you don't have to have a billion-dollar drug at the end. That's incredibly positive for the rare disease space because our technology will be able to lower these costs."

## The many flavors of AI

Though the use of artificial intelligence is permeating all portions of the rare disease continuum including research, diagnosis, drug development, and treatment, within the area of drug discovery and development AI comes in many flavors. The way one drug developer employs AI may be quite different from others. In fact, it has become both a buzzword and a ubiquitous technology throughout the pharmaceutical industry. Recursion Pharmaceuticals, though, may represent one of the more unique AI-driven approaches to drug discovery.

When the Salt Lake City-based drug development company began life as a spinout from the University of Utah at the end of 2014, it did so with a rather bold goal of developing 100 drugs in 10 years by using its AI platform to repurpose drugs for rare disease. The company has since broadened the indications it pursues to go beyond rare diseases and is also looking at novel compounds, but rare disease continues to represent a significant area for the company, including its lead clinical candidates. The fundamental discovery that led to the formation of Recursion is that when genes are "broken"—a mutation prevents them from functioning as they should and a disease state results—human cells begin to look different in many ways. By using machine vision, powerful computers can be trained to spot differences


that may be too subtle for the human eye to see. What's more, these differences can be recognized at a speed that extends well beyond human capability.

Chris Gibson, co-founder and CEO of Recursion Pharmaceuticals, said that the tools that have been developed over the past forty years to understand biology have reached a point where we have solved biology to the extent that humans can hold in their heads and understand. He said we've reached a point where there's declining efficiency of discovery as it has traditionally been carried out. "When you're dealing with a network of tens of thousands

**"It feels like we're right at the beginning of a pretty miraculous set of changes in this industry, which are going to be as disruptive to the fabric of this industry as Uber and Lyft have been in the world of transportation."**

*—Chris Gibson, co-founder and CEO of Recursion Pharmaceuticals*

of genes, hundreds of thousands of proteins, and trillions of interactions every second in every cell in our body between these proteins, that's not something we're going to be able to solve with the capabilities of the human brain," said Gibson. "AI has this pretty incredible ability to synthesize vast quantities of data that are much too big for any human, or any collection of humans, to work through, understand, and to see patterns in that scale of data."

**It is now recognized that small patient populations for rare disease therapies can be economically sustainable.**

Recursion's approach allows it to explore a large number of potential therapies at once. It's looking broadly across biology and has worked on more than 1,700 genetic diseases to date. The company is actively engaged in about 250 of those. Its lead programs in the clinic include an experimental treatment for cerebral cavernous malformation, which is a condition that involves irregular blood vessel formations in the brain that can cause seizures, vision and hearing loss, paralysis, and strokes. The company is also in the clinic with an experimental drug to treat neurofibromatosis type 2, a rare tumor syndrome. In addition, it is conducting enabling studies necessary to advance a third program to the clinic, and is working on dozens of other programs at earlier stages. In some cases, the company is looking beyond repurposing and considering new chemical entities where existing drugs have failed to show promise. All this has been done with a staff of about 130 employees today.

Whether Recursion can advance dozens of programs cost-effectively and bring treatments to patients in a fast and economical way remains to be proven. There is circumstantial evidence that it is on the right track. Less than 18 months after signing a deal with Takeda, the pharmaceutical company licensed multiple discoveries Recursion had made for multiple undisclosed diseases. And Gibson notes the company has focused on building the company's platform during much of the past five years rather than using it to find new treatments for patients. "It feels like we're right at the beginning of a pretty miraculous set of changes in this industry," he said, "which are going to be as disruptive to the fabric of this industry as Uber and Lyft have been in the world of transportation, and autonomous vehicles will be in the world of automakers."

## Challenges of clinical development

There is a bifurcation of innovation in therapeutic development in the rare disease space. At one end there are technology-driven efforts to harness the massive power of artificial intelligence and develop data-driven search to identifying drugs that could be repurposed to treat rare diseases. Proponents of this approach see this as the fastest and most cost-effective way to arrive at treatments for the vast majority of rare diseases, which today remain without an approved treatment. The benefit is that there are a wide number of compounds that are well characterized and have gone through clinical testing to establish their safety. By scouring these compounds to find ones that may have activity in a given rare disease, they can follow a potentially abbreviated path to approval and be made available to patients at far less cost than a novel compound for a small population of patients. At the other end drugmakers are finding they can modulate gene activity with small molecule drugs, address misfolding proteins with chaperones, as well as harness new modalities that elegantly target the

underlying mechanism of a rare disease and interfere with or correct the underlying gene or process producing a pathogenic protein. In some cases, these emerging approaches, which include such things as gene therapy, gene editing, and antisense oligonucleotides, may have the potential to not only treat a genetic condition, but also provide functional cures with a single treatment.

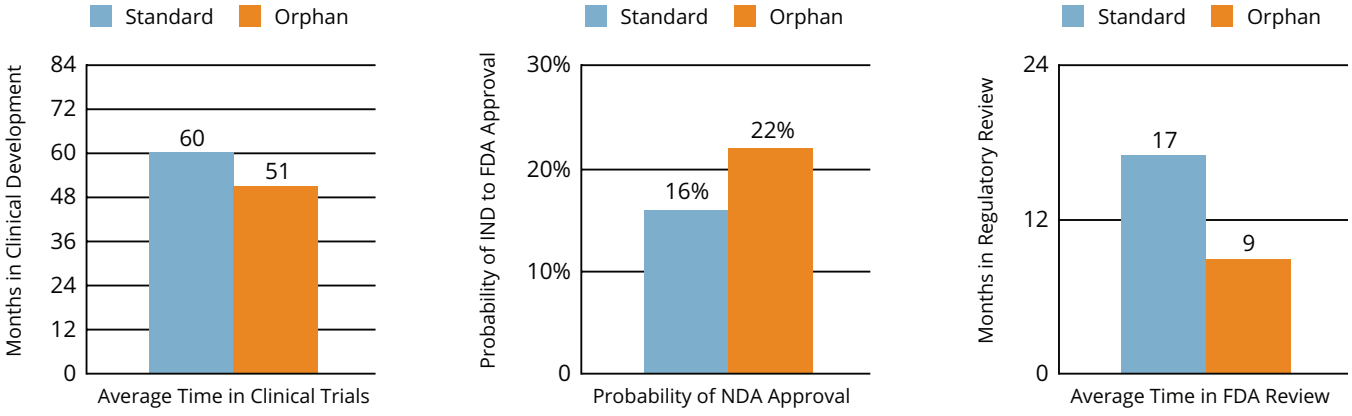
One reason that innovation is flourishing within the rare disease sector is that it is now widely recognized that small patient populations for rare disease therapies can be economically sustainable. While financial incentives, such as the Orphan Drug Act and the Pediatric Rare Disease Priority Review Voucher, have made pursuit of such therapies more attractive to industry, companies and investors have come to recognize there are other financial benefits to pursuing rare disease therapies. These include the opportunity to use relatively small clinical trials to win approval for a rare indication, the precision nature of many rare disease therapies that helps to establish the efficacy of the treatment, and the clear value proposition they can demonstrate with payers necessary to command high prices, all of which can make this an attractive area despite the small patient populations these therapies treat.

Worldwide orphan drug sales are forecast to reach $262 billion in 2024, according to EvaluatePharma's *Orphan Drug Report 2018*. The compounded annual growth rate of orphan drugs between 2018 and 2024 is forecast to be 11.3 percent, about twice that of the non-orphan drug market. By 2024, the industry analysis service forecasts that orphan drugs will represent 21.7 percent of worldwide prescriptions, up from just 16 percent in 2017.

A January 2019 **study** in the *Orphanet Journal of Rare Diseases* [Jayasundrara et. al.] suggested the out-of-pocket clinical costs per approved orphan drug reached $166 million in 2013 dollars as compared to $291 million per non-orphan drug. Those numbers grow to $291 million per approved orphan drug versus $412 million for a non-orphan drug on a capitalized basis. When the authors focused on new molecular entities only, they found that the capitalized clinical cost per approved orphan drug was half that of a non-orphan drug.[16]

Nevertheless, rare disease drug development poses a number of unique challenges. Because of the small population for these conditions, it may be difficult to find participants for a study. The heterogeneity of a rare disease and the way it progresses may not be well understood,

## Drug Development Times: Standard vs. Orphan Drugs



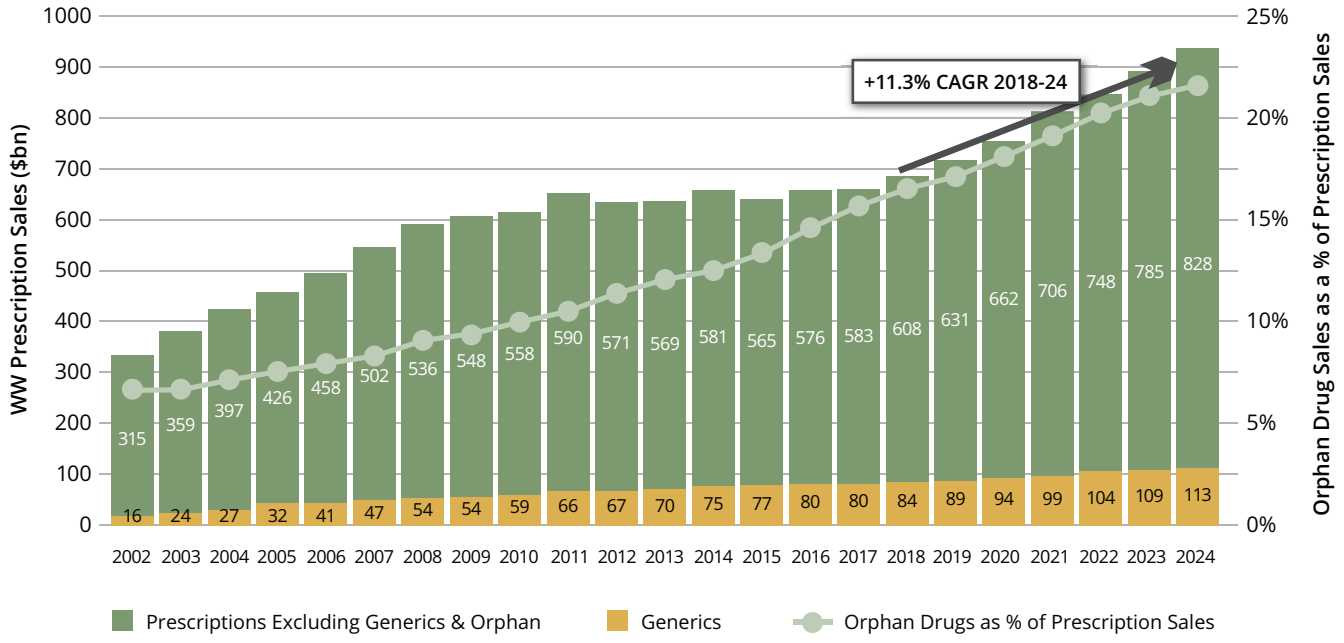

*Source: Premier Research, Orphan Drug & Rare Disease Development: Understanding the U.S. and European Regulatory Landscape, 2015, via Dan Donovan and Tony Howell, "**When the orphan disease patient speaks, listen:** The power of patient-centric digital approaches in orphan drug development and commercialization. Clearpharma.com*

which can stymie drug developers' ability to determine the patient selection criteria or meaningful endpoints for a study. That is why natural histories can play a critical role in drug development. Small patient populations may also be geographically dispersed, and patients may not easily be able to travel to a clinical trial site to participate. And a placebo-controlled clinical trial not only requires additional patients who may be difficult to find, but in the case of a disease where there is no approved therapy, patients may be unwilling to be in a placebo-controlled trial if there is a potential therapy being provided to treat a condition without one.

Under FDA Commissioner Scott Gottlieb, the agency had been working to take several steps to modernize the approach to clinical trials and apply innovative approaches to decentralize studies by using mobile technologies, validating novel endpoints, and streamlining the process. "In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive but disruptive changes that certain innovations can enable," Gottlieb said in a March 2019 statement prior to his stepping down. "We appreciate that scientific and technical complexity is a real and ongoing challenge, but industry and academia also need to invest in and leverage these approaches and develop new incentives that reward collaboration and data sharing across the clinical research enterprise."

Some rare disease organizations aren't waiting for trial sponsors to lead the way. Parent Project Muscular Dystrophy has been working with the Institute for Advanced Clinical Trials for Children to develop a master protocol for Duchenne muscular dystrophy. A master protocol, one of the innovations Gottlieb said the FDA is interested in exploring, has been a topic the rare disease group has been working on for a while. For Duchenne, it would allow multiple therapies to be studied at the same time. Such an approach could use a single placebo control group to study

## Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2002-2024)




*Source: Evaluate Pharma® May 2018*

**"In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive but disruptive changes that certain innovations can enable."**

*—Scott Gottlieb, former commissioner of the U.S. Food and Drug Administration*

multiple drugs in patients with different forms of the disease. "A platform trial may make the clinical trial process more efficient—which is especially important with a rare disease such as Duchenne, which has a small population of patients to recruit," wrote Abby Bronson, senior vice president of research strategy for Parent Project Muscular Dystrophy in a November 2018 post on the organization's website that provided an update on the group's effort. "This has the potential to limit both risk and disappointment."

Technology is being employed to address many of the challenges clinical trials sponsors face in designing and running rare disease studies, not the least of which is finding patients needed to conduct them. A 2018 **study** in the journal *Contemporary Clinical Trials Communications* [Fogel] that explored the various reasons why clinical trials fail found that the inability to enroll an adequate number of subjects is a common problem.[17] One study of 114 trials in the United Kingdom found that only 31 percent achieved enrollment goals. A separate study reported that one-third of publicly funded trials required a time extension because they failed to meet initial recruitment goals.

Beyond the use of innovative trial designs to create greater efficiency, there are a growing number of efforts to incorporate digital health sensors video technology into clinical trials. The use of this technology promises to accelerate the development of new therapies, make participation in clinical trials less disruptive to the lives of patients, and allow for the use of endpoints that are more meaningful to patients. With the ubiquity of smartphones, many people today are walking around with a device capable of monitoring their movements, recording their voice, capturing images, measuring heart rate, and sending that data to the cloud. The smartphone and the advent of digital health devices suggest new ways to capture useful data in clinical trials that can be more comprehensive and less burdensome to patients.

Such devices are also being used to determine new endpoints for studies. The nonprofit ALS Therapy Development Institute entered into a collaboration in 2016 with Denali Therapeutics to investigate potential new endpoints for use in amyotrophic lateral sclerosis (ALS) clinical trials. The Institute and Denali will evaluate and analyze data sets collected by the Institute through its Precision Medicine Program. Currently, most ALS clinical trials use a scale known as the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), a questionnaire utilized by clinicians to evaluate the pace at which a person's disease is advancing. It measures such things as speech, handwriting, walking, breathing, the ability to handle utensils, and other criteria to track motor function. ALS, though, is a heterogeneous disease. Progression rates among patients vary greatly. According to the ALS Therapy Development Institute, it takes about 450 people with ALS tracked for more than a year in a clinical trial using the ALSFRS-R (revised ALSFRS) to measure a statistically significant effect of a potential therapeutic on disease progression. In addition to using a revised rating scale, participants provide ongoing disease progression data from home using speech recordings and wearable sensors that can track motion. "Translating potential treatments for ALS from the lab to clinical trials is a crucial step in solving the huge unmet patient need in ALS," said Steve Perrin, CEO & CSO of the ALS Therapy Development Institute when the collaboration was announced.

**The smartphone and the advent of digital health devices suggest new ways to capture useful data in clinical trials.**

# THE MOTHER OF INVENTION

Christine McSherry's journey on the path to becoming the co-founder and CEO of a contract research organization came with a little push from a top official at the U.S. Food and Drug Administration.

McSherry had attended a meeting at the U.S. Food and Drug Administration around 2013 and used the opportunity to corner top brass about concerns she had over an ongoing study for a promising experimental drug to treat Duchenne muscular dystrophy (DMD), a rare and fatal neuromuscular disease that afflicted her son Jett.

McSherry had started her professional life as a registered nurse, but in 2001 she founded and became executive director of the Jett Foundation after her son was diagnosed with DMD at age 5. When she went to the FDA, Sarepta Therapeutics was conducting a clinical trial of its antisense oligonucleotide Exondys 51.

DMD is caused by a mutation in the gene that codes for the production of dystrophin, an essential protein involved in muscle fiber function. Certain genetic mutations in DMD involve the deletion of exons, which interrupt proper translation of the genetic code into a functional protein.

Exondys 51 is a so-called exon-skipping drug designed to treat DMD patients whose mutations lie in exon 51 of the gene. The drug allows the machinery for producing dystrophin to skip over the faulty portion of the gene and produce a truncated form of dystrophin.

At the time of her meeting, McSherry was concerned that the small trial underway for Exondys 51 relied on the six-minute walk test to demonstrate efficacy. She felt there were clear signs that patients using the drug were having benefits but feared that the six-minute walk test would fail to demonstrate that. The six-minute walk test is a widely used clinical measure of efficacy in neuromuscular diseases. It seeks to show efficacy of a drug by measuring the distance an individual can walk in six minutes on a flat surface. Improvement in the measure from a baseline before the use of a drug is used to demonstrate efficacy. Among other problems with the test is the fact that it is not useful for people who have lost the ability to walk.

McSherry told the FDA officials the kids were doing better. The FDA officials said, "Show us." She held up her phone and half joking asked, "Can I film them on this?" To her surprise, they said that would be fine as long as the videos were not edited.

**Jett and Christine McSherry**

**"One thing that I learned is almost anything can be quantified, as long as you can prove that the methodology behind it is solid and reproducible."**

*—Christine McSherry*

She filmed all 12 boys in the clinical study, as well as a few others who were later enrolled in a safety study. She also interviewed each of them. One boy discussed how since he was using the drug he was once-again able to walk his dog. He had been forced to stop doing so because he lacked the strength to remain standing when his dog pulled on the leash. Another boy was now able to get into his mother's car without anyone providing assistance.

McSherry believed these represented important quality of life benefits the drug provided, and gave children feelings of self-esteem. They were measures that could not be adequately captured in a six-minute walk test.

In August 2015, McSherry made a two-hour presentation to the FDA. The officials in the room were emotionally moved listening to the children talk about their experience. McSherry said that Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research congratulated her and told her at the end of the meeting that she had done what the agency had been trying to get companies to do. The problem was that McSherry's efforts had not been done under the oversight of an institutional review board. The data also lacked quantifi-

ability and was retrospective. As a result, the FDA said it would not incorporate it into the formal materials submitted for the review of Exondys 51. McSherry, however, was given a 10-minute slot to present to the advisory committee that reviewed the drug.

The FDA's approval of Exondys 51's in September 2016 was a matter of controversy. Woodcock pushed through approval of the drug despite the advisory committee's recommendation not to approve it and FDA staff's concerns about a lack of data to demonstrate efficacy.

But as a result of that experience, Woodcock challenged McSherry to start a company that could collect similar data in rare disease studies and work with clinical trial sponsors to do so in a rigorous and quantifiable way. In 2017, she along with Mindy Leffler, another Duchenne mom, launched Casimir Trials, a contract research organization that works to analyze and report rare disease patient and caregiver perspectives and real-world evidence collected remotely.

"We knew that other parents had experienced what we did in other rare diseases where they knew that a drug was working, but the study wasn't designed properly enough or nuanced enough to capture the benefit that patients might be seeing. And to live through that is really agonizing and horrible," said McSherry. "Mindy and I do not want another parent to have to live what we went through."

One of the things Casimir is working to do is to develop new data points and measures that can be used in the review process, and to take advantage of smartphones and other technologies to capture data remotely. Any such measures must be validated, but McSherry is hopeful that the FDA will see Casimir data as helpful, and incorporate it into FDA briefing books and the drug review process.

"One thing that I learned is almost anything can be quantified," she said. "As long as you can prove that the methodology behind it is solid and is reproducible."

"The discovery and development of sensitive endpoints of disease progression may help accelerate all ALS clinical trials."

In some cases, new devices are being created to measure new endpoints. When the company AGTC wanted to conduct a clinical study of an experimental gene therapy for the rare eye disease achromatopsia, it faced a problem. Achromatopsia is a condition in which people lose their ability to perceive color. In talking to patients with the condition, though, the company determined that what would be most meaningful to them would be to have relief from the extreme light sensitivity the condition causes. Historically, within the field of ophthalmology, the one provable endpoint that has been used is a measure of visual acuity, which determines the fine specific vision in the central part of the eye. However, in many eye diseases, it is not the central part of the eye where the problem lies. Retinal specialists have many measures they use to determine function, such as visual field, contrast sensitivity, color vision, or the use of optical coherence tomography, a kind of sonogram of the back of the eye. "While all of these measures are quite familiar to retinal specialists, they're not familiar in the clinical development world in detail like they are familiar with visual acuity," said Sue Washer, CEO of AGTC. "They need to understand how they [measure] change over time and how to compile the data and statistically analyze it in a straightforward way. It takes time, negotiation, and analysis to understand the best way to use these other kinds of tools."

Working with the Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine, AGTC has developed a means of measuring light sensitivity in patients. The combination of hardware and software uses an LED controlled by a computer. The level and intensity of the light is varied repeatedly to determine the level of light the patient finds uncomfortable. The tool has now been incorporated into AGTC's clinical studies of its gene therapy. "The FDA is now more open and more willing to have discussions with developers about novel endpoints. They're also very open, and in fact are pointing many

**"While all of these measures are quite familiar to retinal specialists, they're not familiar in the clinical development world in detail like they are familiar with visual acuity."**

*—Sue Washer, president and CEO at AGTC*

developers to specifically look for patient-reported outcomes, quality of life analysis that can help support products that are making a difference in the patient's life," said Washer. "That's very important and a very positive sign."

## From chronic therapies to cures

AGTC's gene therapy is just one of hundreds of gene therapies that are moving through clinical development. A February 2019 report from the Alliance for Regenerative Medicine found that there were 323 companies worldwide developing regenerative medicine therapies in rare diseases including gene therapies, gene-modified cell therapies, cell therapies, and tissue engineering with a total of 587 therapies in clinical development. Investment in the sector rose to $9.7 billion in 2018, a 48 percent increase over the previous year.

**The potential to correct an underlying defect and deliver a functional cure for rare genetic diseases is before us.**

As a sign of the progress that's been made in the field of gene therapy, large biopharmaceutical companies have been buying their way into the emerging field through big-dollar acquisitions. This includes Pfizer's 2016 acquisition of Bamboo Therapeutics for $645 million, Novartis' 2018 acquisition of AveXis for $8.7 billion, Roche's 2019 acquisition of Spark Therapeutics for $4.8 billion, and Biogen's 2019 acquisition of Nightstar Therapeutics for $800 million. As the first commercial gene therapies have arrived, questions remain about their long-term durability, payers' reception, and new payment models that seek to shift risk to drug companies and spread the cost of one-time therapies over time.

The rare disease field has seen a dramatic migration of treatments from when some of the earliest therapeutic strategies were built around replacement therapies for such things as recombinant enzymes for lysosomal storage disorders or recombinant clotting factors to treat patients with hemophilia. This provided a way to provide the body with a substance it was unable to make adequately on its own as a result of a genetic variant. As science progressed, new strategies emerged that allowed drug makers to interfere with the production of pathogenic proteins or upregulate genes to arrest a disease state by targeting the process of translating the genetic instruction from gene to the production of protein, with such modalities as antisense oligonucleotides. With the emergence of gene therapies, gene editing, and other regenerative therapies, the potential to correct an underlying defect and deliver a functional cure for rare genetic diseases is before us.

The rapid pace of therapeutic innovation can be seen in the area of spinal muscular atrophy (SMA), a rare genetic disease characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, individuals with the most severe type of SMA can become paralyzed and have difficulty performing basic functions of life, like breathing and swallowing. People with type 1 SMA, a life-threatening form, produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. It is the leading genetic cause of death for infants. At the end of 2016, the FDA approved Spinraza, making it the first treatment marketed for the condition.

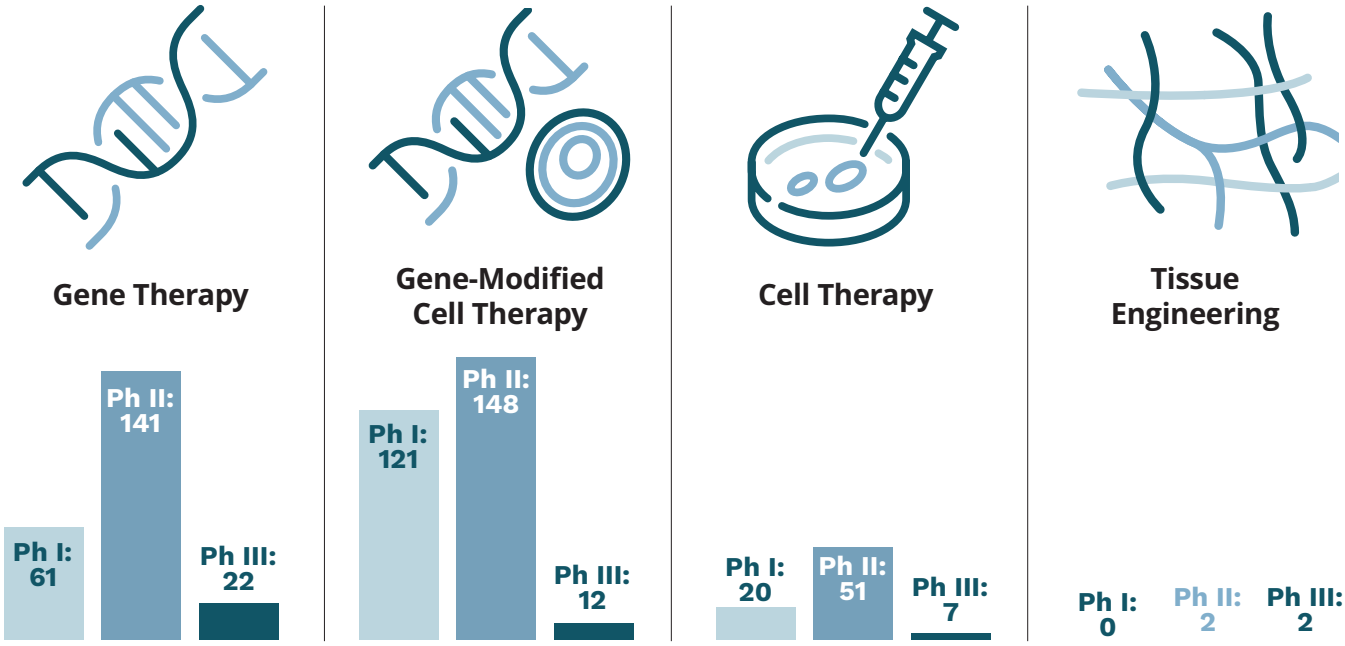
Spinraza, like a growing number of rare disease therapies, resulted from work performed by researchers funded by a patient advocacy group. CureSMA funded early work on the drug, which was developed by Ionis Pharmaceuticals and Biogen. Spinraza is a splice-modulating antisense oligonucleotide that works by binding with messenger RNA to upregulate the SMN2 gene, a backup for the SMN1 gene that is dysfunctional in SMA patients, and get it to produce the protein that the SMN1 gene normally produces. The treatment costs $750,000 in the first year and $350,000 every year thereafter.

Novartis' subsidiary AveXis developed Zolgensma, a gene therapy for SMA. A one-time infusion of Zolgensma for type 1 SMA is designed to address the genetic cause of the condition and prevent further muscle degeneration by providing a functional copy of the human SMN gene to halt disease progression through sustained SMN protein expression. The FDA approved Zolgensma in May 2019. It carries a price tag of $2.1 million, paid over five years, for a one-time treatment.

At the time of this writing, Roche was also advancing risdiplam, an experimental small molecule therapy as a treatment for SMA. The company was expected to file for FDA approval in the second half of 2019. Risdiplam is believed to upregulate the production of the SMN protein by the SMN2 gene to offset the deficiency in SMA patients. In May 2019 at the 71st American Academy of Neurology Annual Meeting, Roche reported encouraging results from pivotal studies that showed patients with type 1 SMA achieved key motor milestones after one year of treatment with risdiplam. While it is not known how Roche would price the drug, it appears SMA will become an increasingly competitive landscape with treatment choices for patients.

While such therapies offer the type of promise rare disease patients could only dream about a few years ago, it's unclear how accessible such therapies will be given their high costs. The durability of these treatments is also unknown. It's unclear whether these therapies will continue to provide benefit to patients over many years or if the

## Regenerative Medicine Trials in Rare Disease as of December 2018




*Source: Alliance for Regenerative Medicine: Regenerative Medicine & Rare Disease February 2019*

**It appears SMA will become an increasingly competitive landscape with treatment choices for patients.**

improvements that have been demonstrated in clinical studies will fade over time.

While there is a growing pipeline of gene therapies, some technologists are developing relatively low-cost devices that don't cure or slow the progression of disease, but provide a potential means for people with debilitating rare diseases to do things they are no longer able to do as a result of their conditions, such as speak, walk, and see.

One example of this is eSight, which has developed electronic glasses to enhance eyesight for people with a number of different conditions including the rare diseases Leber congenital amaurosis, Stargardt's disease, cone-rod dystrophy, and a number of other common and rare conditions. The eSight device is a pair of electronic glasses that restores or enhances sight for individuals living with vision loss. Worn like a normal pair of eyeglasses, or with prescription lenses built-in, they allow a person with low vision to see in virtually the same manner as someone who is fully sighted. The device houses a high-speed, high-definition camera that captures everything the wearer is looking at. The footage is optimized and enhanced by clinically validated algorithms that then appears on two, near-to-eye screens in real time. The user can refine the image and zoom, adjust contrast, and focus with a handheld optical trackpad. The eSight glasses sell for $5,950.

Another area that shows promise in this type of assistive technology is the area of muscle diseases. Though exoskeleton suits are being designed for applications for such things as providing soldiers and warehouse workers superhuman strength and stamina, the same technology is being developed for people with neuromuscular conditions.

Talem Technologies's Maestro is a mobile arm that can provide mobility, freedom, and

independence to people with neuromuscular conditions. And Marsi Bionics created the world's first child exoskeleton, which allows a child with spinal muscular atrophy and other neuromuscular conditions the ability to walk. The exoskeleton consists of long support rods that are adjusted to fit around a child's legs and torso. There are motors in the joints that mimic human muscles and give the child the strength to stand upright and walk. The device also includes sensors, a movement controller, and a battery with five hours of life. Because a child with neuromuscular illness will change over time, the exoskeleton can adapt to these changes. The intelligent joints alter the brace's rigidity and automatically adapt to the symptoms of each individual child when required. The company is currently certifying its exoskeletons as medical devices and without reimbursement, it is expected to sell for about $56,000 (€50,000).

The same way in which patients and technology are reshaping diagnosis, research, and therapeutic development, they are also coming together to alter the delivery of care and also ensure that clinical insights into rare diseases feed back into the other elements of the rare disease ecosystem, being a source of data gathering, access to patients for clinical trials, and new insights into the manifestation of a given condition, its progression, and the needs of the patients who suffer from it. Given the complexity of many rare diseases and the need to access multiple specialists, patient groups have been creating comprehensive care models and establishing standards of care for the treatment of rare diseases. ■

# THE DOCTOR WILL SEE YOU

**"A lot of hospitals are driving toward how many billable units they can do. For a hospital to embrace the thought of creating a multidisciplinary clinic when the previous model had decreased efficiency of their staff and providers by 50 percent, you can imagine nobody was going to raise their hand and say, 'Oh, let's do that again.' "**

*—Kelly Ranallo, founder and president of the Turner Syndrome Global Alliance*

At Rady Children's Hospital in San Diego, the neonatal intensive care unit and pediatric intensive care unit were exploring whether rapid genome sequencing could be used to diagnose patients and improve outcomes. One of the babies was in liver failure and was at high risk of bleeding into his brain because of a coagulopathy, an impaired ability to clot. A whole genome sequence of the infant revealed that he had a condition known as hemophagocytic lymphohistiocytosis (HLH), an inherited immune system disorder that is treatable. "We gave him steroids," said Stephen Kingsmore, CEO of Rady Children's Institute for Genomic Medicine. "His liver function recovered, his coagulopathy went away, and he went home instead of dying."

Rady Children's had been making a push to take advantage of new sequencing technology to improve care for infants in the neonatal intensive care unit. In 2011, using pioneering technology and workflow modifications, doctors demonstrated in eight patients that they were able to shorten the time it took to arrive at a diagnosis through whole genome sequencing to just two days from what had previously been a matter of months. With such speed, there would be potential to act on the diagnosis in the NICU and intervene to save children's lives.

Building on that early work, investigators at the hospital in May 2015 published a **paper** in the journal *The Lancet Respiratory Medicine* [Willig et al.] on the use of rapid genome sequencing on 35 infants younger than four months old with a suspected genetic disorder in the neonatal intensive care unit and pediatric intensive care unit between 2011 and 2015.[18] Investigators compared the results to what they found using conventional standard of care testing. The genome sequencing had a 57 percent rate of diagnosis compared to just 9 percent for traditional genetic testing, and 31 percent of the cases had a change in the way doctors managed the patient because of that information. In 11 percent of the cases,

outcomes were changed. In the case of the infant with HLH, doctors saved a life as a result of the information that was made available because sequencing was used. "That was when the world changed," said Kingsmore. "That was when we realized we've not just invented something; we can have a phenomenal impact on hospital course in these babies."

Rady Children's has continued to build on its work. In 2019, it was able to decode a patient's entire genome in 19 hours using artificial intelligence. Now, about one in three children will get a diagnosis when the hospital sequences a genome, one in four will have a change in management as a result, and one in five will have a change in outcome. Kingsmore said that's not just at Rady Children's but across the globe based on 19 studies in more than 700 subjects.

The clinical utility of rapid whole genome sequencing has been compelling enough in the NICU that in September 2018 Rady Children's launched Project Baby Bear, the first California state-funded program to offer rapid whole genome sequencing for critically-ill newborns. The $2 million Medi-Cal pilot program will provide genome testing for babies hospitalized in intensive care. The effort will make use of whole genome sequencing conducted by Rady Children's Institute for Genomic Medicine as a first-line diagnostic test done for babies at four participating hospitals statewide. The project seeks to demonstrate that the technology provides a cost-effective means to diagnose genetic conditions and more efficiently guide clinician treatment decisions.

## A gap in knowledge

While clinical uses of whole genome sequencing are beginning to make their way into practice today at places like Rady Children's, the technology may be moving faster than physicians, who face a gap in their education about genetics. In fact, an October 2015 **article** in the journal *Advances in Medical Education and Practice* [Wolyniak et. al] reported that as of 2013, about half of available medical genetics

# Consortium Aims to Expand Access to Clinical Whole Genome Sequencing

In 2019, eight healthcare and research organizations in the United States and Canada launched the Medical Genome Initiative, a consortium working to expand access to high-quality clinical whole genome sequencing for the diagnosis of genetic diseases.

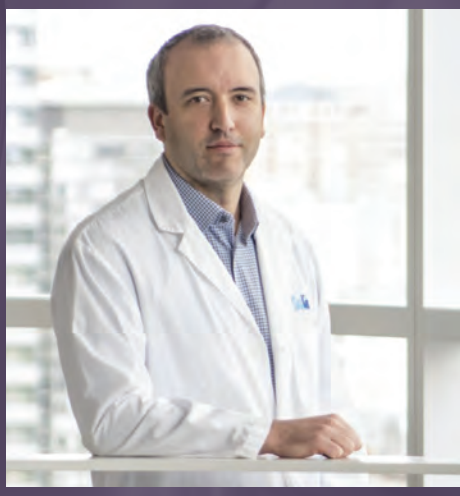
The Initiative will focus on the publication of common laboratory and clinical best practices for the application of clinical whole genome sequencing.

Founding member institutions of the Medical Genome Initiative include Baylor Genetics, Broad Institute of MIT and Harvard, HudsonAlpha Institute for Biotechnology, Illumina, Mayo Clinic, Rady Children's Institute for Genomic Medicine, The Hospital for Sick Children, and Stanford Medicine.

Initial topic areas of focus for the Initiative include clinical whole genome sequencing analytical validity, clinical utility measures, clinical data infrastructure, and data sharing.

The consortium said early deployment of clinical whole genome sequencing has the potential to deliver precise molecular diagnosis and reduce the number of unresolved, complex, costly, and chronic genetic disease cases, especially for newborns and children. But for the technology to be implemented at scale, recommended best practices are useful to guide the clinical community.

"Emerging evidence on [clinical whole genome sequencing] is positive, but clinical laboratories and healthcare systems looking to implement this technology for genetic-disease populations lack recommended best practices to inform test validation and deployment," says Christian Marshall, co-director of the Centre for Genetic Medicine at SickKids and chair of the Medical Genome Initiative. "By coming together, the Initiative can provide an informed perspective on how to best implement this promising new technology and measure its utility."



**Christian Marshall, co-director of the Centre for Genetic Medicine at SickKids and chair of the Medical Genome Initiative**

**"That was when we realized we've not just invented something; we can have a phenomenal impact on hospital course in these babies."**

*—Stephen Kingsmore, president and CEO of Rady Children's Institute for Genomic Medicine*

residencies remained vacant, a statistic the authors called "sobering" given the "increasing need for medical professionals who can bring new genetic technologies into common practice."[19] Surveys of third- and fourth-year American and Canadian medical students suggested that only 26 percent were learning genetics as a part of their formal clinical training while more than 50 percent lacked basic competencies related to applying genetic tools to prospective patient care.

Among academic family physicians, the authors said 54 percent felt that they were not knowledgeable about available genetic tests. They lacked an understanding of when to recommend a patient to a genetic counselor, an awareness of online genetics resources like the United States National Institutes of Health's Online Mendelian Inheritance in Man, and the appropriate situations in which to refer patients to genetics specialists. "As genomic data become more readily available to medical professionals," the authors wrote, "it becomes essential that not only specialists, but also primary care providers be conversant in how to use modern genetics and genomics tools to make treatment decisions for their patients."

**Among academic physicians, 54 percent felt that they were not knowledgeable about available genetic tests.**

## In search of excellence

Because of the complexity of many rare diseases, patients and their families are not only tasked with finding a doctor with the expertise to treat a given condition, but oftentimes a battery of specialists who can manage the many different aspects of a rare disease. Patients can be forced to navigate the healthcare system in search of appropriate physicians, face difficulty getting seen in a timely manner, and may have to travel great distances to obtain the specialized care they need.

When an endocrinologist diagnosed Allie Ranallo at age 8 with Turner syndrome, a chromosomal disorder that affects only females, her mother Kelly was faced with figuring out how to get the care her daughter needed. In addition to short stature, Turner syndrome can affect the heart, kidneys, hearing, skin, and vision, and cause learning disabilities. "We went from having a single pediatrician to trying to find, coordinate, and get access to about eight specialists in a one- to two-month period of time," said Ranallo. "One of the biggest challenges is that nobody is there to help you navigate that. You go back to your pediatrician, who's supposed to be your quarterback, but your pediatrician doesn't understand the condition and didn't recognize it for eight-and-a-half years."

Over time, Ranallo worked with Mercy Children's Hospital in Kansas City, Missouri to create Children's Mercy's Turner Syndrome Clinic, Great HeighTS Clinic. There were a few other Turner syndrome clinics established, which she looked to as models, but she also saw opportunities to improve on them. Three times a year, 45 to 60 girls with Turner syndrome from about six different states gather at the clinic to see a team of specialists to address all of these girls' medical needs. At the end of the day, the team of doctors will meet to discuss each patient.

The hospital was initially resistant to the idea of the multidisciplinary clinic for Turner syndrome. Ranallo said that it takes a lot of effort to understand the cultural environment and the challenges that stand as barriers to such a clinic. The hospital already had some experience with multidisciplinary clinics. When Ranallo spoke to specialists about creating one for Turner syndrome, they told her they would

love to because it would improve outcomes, but when they tried such a clinic in the past, it decreased their efficiency by 50 percent. "A lot of hospitals are driving toward how many billable units they can do," said Ranallo. "For a hospital to embrace the thought of creating a multidisciplinary clinic when the previous model had decreased efficiency of their staff and providers by 50 percent, you can imagine nobody was going to raise their hand and say, 'Oh, let's do that again.'"

When a group of stakeholders came together to discuss the clinic, they addressed previous problems the hospital had. In the past, the hospital put a patient in a room for six hours, and one specialist after the other would come in. If one took longer than expected, it backed up the others. If a patient failed to show up, a slate of appointments with half a dozen doctors were lost. Instead of isolating the patients, Mercy's Great HeighTS clinic keeps all of the patients in a community waiting room. The Turner Syndrome Global Alliance, which Ranallo co-founded, schedules educational programing during the clinics, including a luncheon speaker, and the clinics have become social gatherings that the girls look forward to because they do things such as arts and crafts, or have their hair and nails done.

The success of the clinic has spawned others, both within Turner syndrome and in other conditions. A sister Turner syndrome clinic in Wichita doesn't have all of the same specialists. To build out the educational component, they are using Skype to livestream educational content. Girls with Turner syndrome are susceptible to infertility. A gynecologist isn't available at the Wichita clinic. To avoid requiring patients to travel to the Kansas City clinic, the clinic is in the process of installing telemedicine technology for remote consultations and they are exploring using that to minimize some of the visits for patients who must travel long distances.

Many patient groups have pursued this model of clinical care. The Tuberous Sclerosis Alliance has been working to help establish clinics throughout the country in the hopes that no patient with tuberous sclerosis complex (TSC) would need to travel more than four hours to obtain care. The organization said there are now 64 TSC clinics nationwide to treat the complex condition, a genetic disorder that causes tumors to form in many different organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. The condition is associated with seizures, developmental delay, intellectual disability, and autism. Patients may need the care of a cardiologist, neurologist, nephrologist, dermatologist, pulmonologist, psychiatrist, and dentist.

**Allie and Kelly Ranallo**

"We have clinical consensus guidelines that were developed in 1999 and updated in 2011 and again in 2018. We ask and require that clinics that are designated by the TS Alliance follow those clinical consensus guidelines," said Kari Luther Rosbeck, president and CEO of the TS Alliance. "We hope these are leading to improved quality of life for individuals living with TSC. The next thing we'd like to do is look at evidenced-based standards of care so you know if you follow this course, you will have an improved quality of care."

There are 18 clinics that are currently entering data into a TS Alliance natural history study, which today includes 2,200 patients. The organization makes the data available to

**"The next thing we'd like to do is look at evidence-based standards of care so you know if you follow this course, you will have an improved quality of care."**

*—Kari Luther Rosbeck, president and CEO of the Tuberous Sclerosis Alliance*

researchers. The directors of all of the clinics come together for an annual meeting in conjunction with the American Epilepsy Society meeting to exchange information. Physician meetings are also held at the TS Alliance world patient conferences. Starting in 2018, the organization introduced a meeting for the clinic nurse coordinators during its conference.

While the TS Alliance is hoping to see telehealth incorporated into the clinics to expand their reach, efforts to do so are complicated both by state licensing requirements and reimbursement issues that create challenges to implementing any such services. It's been part of the TS Alliance strategic plan for some time. Some centers offer it within their own state, but there are licensing requirements that prevent them from offering it to patients outside their state. "Telehealth is very complicated and doesn't have the laws and rules around it yet," said Rosbeck. "Payer engagement around it has not caught up with where we need to be. We would love to do more. We're waiting for the regulators and the payers to catch up."

## Bridging gulfs

Despite such complications, digital health technologies are working their way into the rare disease landscape. One way this technology is being used is to drive expertise to where the patients are. That was the idea when the Ehlers-Danlos society in 2019 launched an effort in partnership with Project ECHO to create a program that provides presentations and discussions through an online conference call platform to physicians treating patients with the rare connective tissue disorders Ehlers-Danlos syndromes (EDS) and hypermobility spectrum disorders (HSD). The group launched hubs in the United States and the United Kingdom to host 90-minute teleECHO clinics on a weekly basis with a range of topics covered over a nine-week rotation.

Lara Bloom, international executive director for The Ehlers-Danlos Society said the programs are a way to address the lack of knowledge among physicians that patients encounter when they seek care. "Too many in our community report that they are forced to travel far and wide to access a physician who knows how to manage their healthcare, often at great personal expense, and often with incredibly long wait times–some must wait over two years," she said. "Project ECHO can help us reach clinicians anywhere in the world, arming them with the tools and knowledge to care for their own patients with EDS and HSD."

In addition to educating physicians and allowing rare disease patients to overcome some of the challenges of cost and geography, other digital health technologies are being deployed to monitor patients remotely, gather data to provide a greater understanding of specific rare disease conditions, and provide patients with better access to their own health information.

The Marfan Foundation and the digital health company Backpack Health in 2018 announced a partnership that enables the foundation to create a patient registry. Patients receive customized information to manage and support their care, while the foundation has access to de-identified and aggregated data that researchers can leverage. Patients who join the registry get free access to Backpack Health's upgraded subscription to help manage their healthcare records. The personal health

# CARING FOR THE CAREGIVER

Caregivers have long been among the least visible and most critical elements of the healthcare system. A 2018 study, the first of its kind to look at caregivers for rare disease patients, suggests their needs are often ignored by providers, drugmakers, and themselves.

About half of the respondents report that they have had a doctor, nurse, or social worker ask what was needed to provide care to the recipient, and just one in four have had these discussions about their own care needs.

Rare caregivers often are required to perform medical and nursing tasks without training. The report recommends that paid medical care teams should identify the primary caregiver and ensure they are documented and included in plans for treatment.

One in four rare caregivers report that the person they care for has participated in a clinical trial. In those cases, the rare caregiver often completes paperwork, provides transportation, fills out trial response documents, and coordinates care.

The report suggests drug and device manufacturers should consider how the presence or absence of a family caregiver impacts the development process. They should also identify ways to capture the perspective of the caregiver, including their role in medication or device management, and the impact of disease on unpaid caregivers.

Finally, caregivers do a poor job of caring for their own needs. Only 33 percent use paid help or aides, and only about one in five have used respite care, professional support to provide the regular caregiver a break from their responsibilities. Two-thirds of rare caregivers say they find it difficult to maintain their own health.

The National Alliance for Caregiving in partnership with the rare disease patient advocacy organization Global Genes commissioned the study, which was based on an online survey of more than 1,400 caregivers of individuals with more than 400 different rare diseases conducted in late 2017 by Greenwald & Associates.

records tool works on any device to make information manageable, shareable, portable, and translatable. It collects, manages, and stores health records across multiple providers in five languages. Backpack has entered into similar partnerships with other rare disease groups including the Ehlers-Danlos Society and the National Adrenal Diseases Foundation.

There is a virtuous circle in rare disease. Real world data from care can feed back to research to improve diagnosis and help find treatments. That in turn leads to improvements in care. At the center of this are patients, who are driving these efforts enabled by technology that can gather, aggregate, and analyze data in ways that would have been not possible a decade ago. ■

# IMAGINING THE FUTURE

**"We have a view of rare disease research, everything from basic gene discovery to applications of these drugs in the community, in a much more global, holistic way. When we look out at the landscape, it is blindingly obvious to us that they are the same problems. We look across these problems in disease after disease and patient group after patient group. They all think that it's different. We as human beings emphasize the differences. That is the secret of our demise."**

*—Christopher Austin, director of the National Center for Advancing Translational Science*

Researchers at Children's Hospital of Philadelphia (CHOP) and Penn Medicine reported that they were able to use CRISPR gene editing in utero in a mouse model to correct a genetic mutation that results in a lung disease that causes death within hours of birth. The investigators reported their findings in an April 2019 **study** in *Science Translational Medicine* [Alapati et al.].[20] There are many reasons why being able to intervene to correct a pathogenic genetic mutation in the womb is an enticing prospect. Though such interventions are not a part of clinical practice today, it is not difficult to imagine a future where genetic diseases are not only diagnosed in the womb but corrected as well. "This is not a panacea for curing every genetic disease that's out there," study co-leader William Peranteau, an investigator at CHOP's Center for Fetal Research, and a pediatric and fetal surgeon in CHOP's Center for Fetal Diagnosis and Treatment told **Wired**.[21] "At some point in the future—not tomorrow or the next day, years from now—I think in utero editing would provide hope for families that today have none."

Biomedical advances are moving at a rapid pace and accelerating with the convergence of emerging information technologies such as artificial intelligence and digital health, and with advances in the ability to understand and edit, manipulate, and alter the genetics of an individual. This year the rare disease community saw the approval of Zolgensma, the first gene therapy approved to treat spinal muscular atrophy, a disease that in its most severe form robs infants of their lives before the age of 2 or requires breathing support. As members of the rare disease community contemplate ways to improve the diagnosis and treatment of rare diseases,

**"What we see is the uncertainty of getting this information, and what the information will do to our lives. The question is, 'How much are we willing to learn about ourselves?' "**

*—Stephen Groft, senior advisor to the director of the National Center for Advancing Translational Sciences*

there is an opportunity to change the grim prospects many rare disease patients face today. Science and technology, though, may be the least of the obstacles the rare disease community will need to contend with if it is to realize the potential that is before it today.

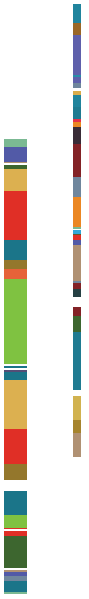
There are two futures before us. One future is driven by our ability to harness massive stores of genetic, medical, and a range of 'omic data to understand the relationship between genotype and phenotype, and provide rapid diagnosis. There is great optimism about eliminating the protracted diagnostic odyssey for rare disease patients where a pathogenic gene is known. The integration of artificial intelligence, the emergence of regenerative therapies, and the means to precisely disrupt the genetic machinery of rare diseases promise to accelerate the pace of therapeutic development and make available a range of new therapies to treat patients who today are without approved medicines—not only treatments for many more patients, but in some cases functional cures.

The other future is one of stalled progress where the technologic and scientific advances are not capitalized on because of a failure to address obstacles that threaten to slow advances, hamper the development of new therapies, and impede access to treatments and care. This includes failure to develop and adopt new ways of doing things to address the unique nature of some advancing therapies for treating rare diseases, including new research, business, regulatory, pricing, and treatment models. Failing to do so will leave millions of rare disease patients and their families unable to benefit from the advances happening every day.

## Driving progress with data

The falling cost of whole genome sequencing has the potential to expand its use and propel the technology into routine clinical applications. Then-Illumina CEO Jay Flatley at the 2017 J.P. Morgan Healthcare Conference spoke about the company's plans to drive the cost of genome sequencing down to $100. In fact, we are on a path to make whole genome sequencing at birth affordable as a newborn screening tool. There are compelling arguments for doing so, but barriers will remain. While it's not difficult to convince someone with a rare disease of the utility of such screening at birth as affordable, many people may not want to learn what a genome has to tell them outside of an immediate and actionable diagnosis. In addition, many people remain concerned about privacy. Despite the Genetic Information Non-Discrimination Act of 2008, which addresses discrimination by health insurers and employers, people remain concerned about the misuses of their genetic information and the potential for it to be used to harm them. "What we see is the uncertainty of getting this information, and what that information will do to our lives," said Stephen Groft, senior advisor to the director of the National Center for Advancing Translational Sciences at the National Institutes of Health. "The question is, 'How much are we willing to learn about ourselves, and at what stage?' I think society will be discussing this more in the very near future, especially as the price continues to come down and the accuracy improves."

Additional policy protections and public education are needed to catch up to the pace at which the technology is moving. In an August 2018 **report** from the Hastings Center



**We are on a path to make whole genome sequencing at birth affordable as a newborn screening tool.**

# REALIZING OPPORTUNITIES

When people talk about innovation in regard to rare diseases, often the focus is on technology, referring to such things as gene therapy, next-generation sequencing, or artificial intelligence. While the dizzying array of technologies before us are transforming the rare disease space, innovation will be necessary throughout the rare disease ecosystem if the rare disease community is to realize the opportunities to improve the diagnosis and treatment of disease that is before us today.

- Technology is not a solution in and of itself. It can enable great advances, but patient advocacy will be one of the critical drivers of employing the technology in ways that can reduce the time and cost of research, diagnosis, therapeutic development, and treatment.

- The proliferation of data is enabling new advances in rare diseases. Access to large data sets will be critical for making advances in rare diseases, but a lack of data sharing threatens to undermine progress. Patients must be able to exert influence and control, when appropriate, over the use of their data to enable rapid and precise research developments. They should insist on consent agreements or the use of dynamic consents that give them authority over how their data can be used in the future.

- Data and biosamples are essential for researchers to understand rare diseases and advance the development of new therapies. Awareness of the importance of these elements needs to be communicated to patients so they understand the significance of making these available to researchers.

- Regulatory incentives reward successful development of rare disease therapies, but smaller drug developers face challenges in the early stages of preclinical and early clinical development. Incentives need to be adjusted so that smaller drug companies, that are targeting smaller patient populations can address challenges early in the development process and successfully develop and deploy therapies.

- Regulators and payers have different needs to satisfy. Regulators need to be convinced that a therapy is safe and effective. Payers need to be convinced that therapies are not only safe and effective but provide value. It will take evidence of efficacy and clinical impact to make the case for both regulators and payers to ensure patients have access to needed therapies.

- Because the durability and efficacy of some new therapies may not be well known, drug companies will need to share risk with payers if they hope to get value for innovative therapies.

- Repurposing is a critical strategy to advance the availability of treatments for rare diseases where there may be no available therapies today.

- Drug makers will need to deliver true innovation as pricing of therapies will continue to come under greater scrutiny. The strategy of winning by repurposing generic drugs for rare indications and attaching high price tags to them will not work.

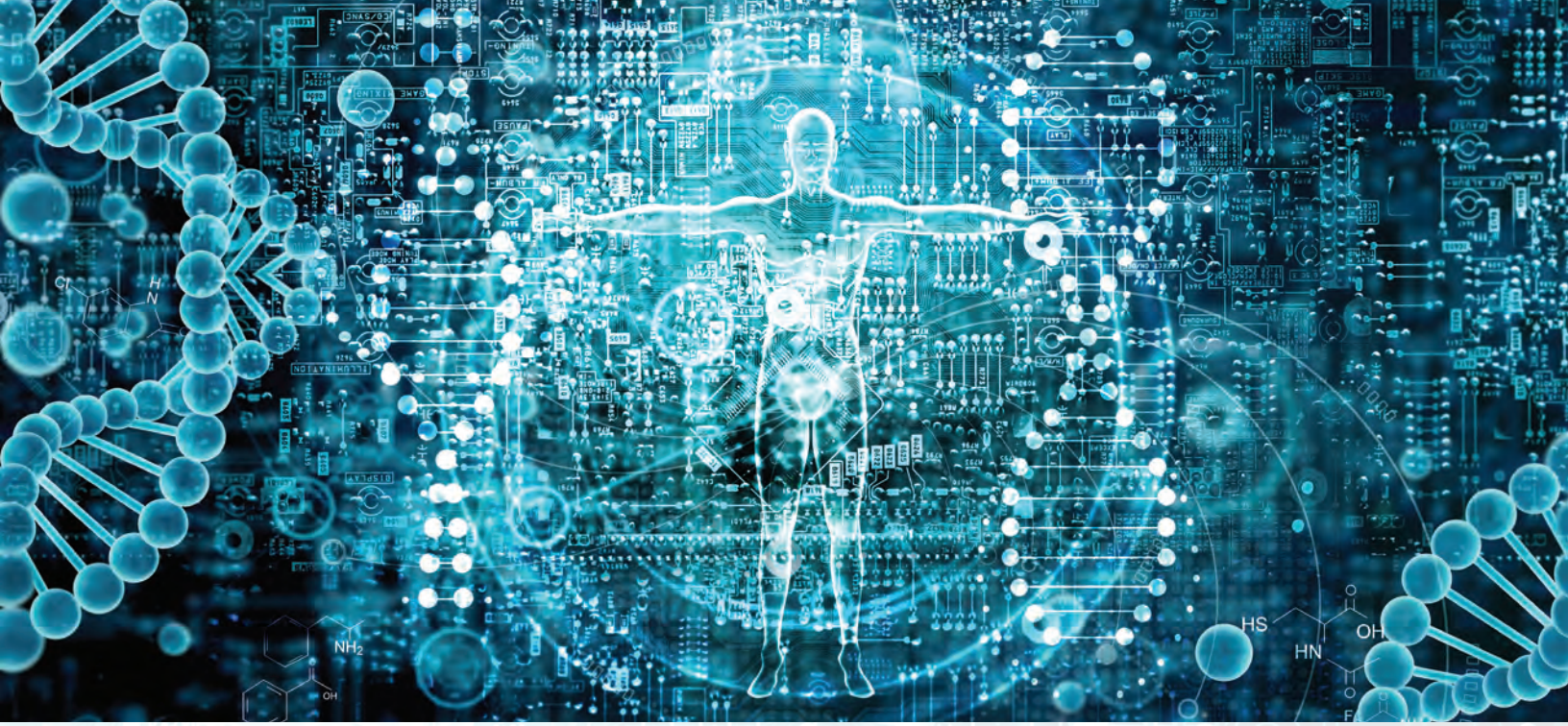
- There is a need to harness innovation to reduce the cost of drug development to help increase the economic sustainability of the pursuit of novel therapies for rare diseases.

- The traditional drug development, manufacturing, and distribution model will not be sustainable for diseases with only a handful of patients or an N-of-1 disease. New models will be needed to deliver safe and effective therapies for these patients.

- The potential for a programmable approach to gene therapies and antisense oligonucleotides offers the ability to mix and match a toolkit of vectors to customize therapies for patients, but new regulatory, business, manufacturing, and delivery models will be needed to enable such possibilities.

- Rare disease patients and organizations should recognize their shared interest and challenges across related and unrelated rare diseases.

- Assistive technologies won't address a patient's underlying disease but have a big potential to




improve quality of life for patients in a cost-effective manner and enable patients otherwise unable to move, speak, and see to do so.

- New manufacturing methods are needed to allow for small patient populations and to address challenges of supply chain issues to getting certain rare disease therapies in the developing world.
- Informed consent agreements need to be broadened to contemplate potential future uses and also to ensure patients have rights to their own data and materials and the freedom to share it with whomever they choose.
- Privacy protections, such as the Health Insurance Portability and Accountability Act's privacy rule and The Genetic Information Nondiscrimination Act, should be revisited to ensure they are protecting people's privacy as intended, but also not unintentionally hampering progress in research.
- At one time when physicians didn't have the ability to accurately diagnose and treat rare, genetic diseases, the admonishment "when hearing hoofbeats think horses not zebras" is outdated. Doctors need to know when to think about genetic disease and how to go about diagnosing and referring such patients to appropriate specialists.
- Artificial intelligence systems have the potential to address a gap in frontline physicians' ability to recognize rare disease by helping identify when such possibilities should be considered and pointing to the correct diagnostic pathway to pursue.
- There is a human resource gap that needs to be addressed with regards to genetic medicine. New and existing doctors require training and a growing number of genetic counselors will need to be brought into the field to help patients understand.
- Telehealth and remote monitoring technologies hold the promise of bridging geographic gulfs in patients getting access to specialized care and participating in clinical trials. Regulatory barriers to deploying this technology need to be addressed.
- Time and money are precious commodities for rare disease advocates. Collaboration is critical. By focusing on shared goals rather than competing against each other, progress can be accelerated, redundancy avoided, and more can be accomplished.
- Rare disease is a global problem, but many rare disease patients do not enjoy the advances that have been realized to date. It will be necessary to find ways to improve access to available therapies and emerging technologies so rare disease patients in resource-limited communities throughout the world can benefit.

**"It's important to break through those silos because the larger the net we can use, the quicker we'll get answers."**

*—George Church, co-founder of Nebula Genomics*

[Johnston et al], bioethicists argued against genome-wide sequencing of all newborns because the results are not well enough understood, the need to interpret results could strain resources, and the findings could cause parents to have undue anxiety about the health of their children.[22] Bioethical considerations aside, payers remain a barrier to accessing whole genome sequencing and there is a need to validate the cost-effectiveness of the clinical use of the technology and ensure its robustness in clinical practice.

## Breaking down silos

In an era of data-driven, genomic medicine, access to large data sets is essential to closing gaps in the understanding of rare diseases. Some countries have been working to rapidly incorporate the technology into clinical practice. In 2013, the United Kingdom established Genomics England to conduct the 100,000 Genomes Project, an effort to sequence a large group of patients with cancer and rare diseases and their families. Building on Genomics England's work, England's National Health Service in October 2018 became the first health service in the world to routinely bring sequencing into healthcare in a move toward precision medicine. It established seven genomic hubs to conduct genetic testing, a lab in Cambridge to perform whole genome sequencing, and 13 national genomic medicine centers that draw on multidisciplinary teams to analyze and report results.

As the cost of sequencing continues to fall and there is a proliferation of genomic data, one concern among researchers is that the potential to capitalize on the vast amount of data is being stymied by resistance to share the data with others among hospitals, academic centers, corporations, and other institutions that hold it. In some cases, this may be because of the absence of consent from patients, privacy concerns, or the desire to hold the data as an economic and competitive advantage. "It's important to break through those silos," said genomics pioneer and co-founder of Nebula Genomics George Church, "because the larger the net we can use, the quicker we'll get answers."

While there are initiatives around the globe to drive data sharing, the siloing of data remains a substantial concern and is widely seen as an obstacle to improving diagnosis and increasing treatments for rare diseases. Part of the problem is the need for better infrastructure to enable data sharing among researchers by making it easier to for them to apply for data and use it. There's also a need for broadening patient consent to look beyond current need and contemplate potential future uses of an individual's data to allow its use beyond a single study and a single disease. "Probably the biggest challenge at the moment is the lack of good infrastructure for genomic data sharing," said Daniel MacArthur, co-director of medical and population genetics at the Broad Institute. "The current NIH-mandated system for data sharing, which is called the Database of Genotypes and Phenotypes (dbGaP), is wildly inadequate for the growing amount of data that's been generated across an enormous range of different diseases, and doesn't currently serve the needs of the community and get the data out to all of the researchers that would be able to make use of it."

MacArthur thinks we're at a fork in the road and have a choice of two paths. At one end is the path of despair, which is the path, he says is being followed in the case of our

electronic medical records where a relatively small number of commercial providers have gained a monopoly over that entire system. As a result, transferring patients' data from one place to another is not just hard, it's actively inhibited by the systems that have been built to store that data. "They actively work to make it difficult for patients to move their data from one place to another," he said.

The other path that we could follow he likens to what we see on the web, a system that is focused on open standards and interoperability between systems. "If we follow that path, then that results in a community where data can be shared relatively openly and rapidly, but also responsibly," he said. "Many of us think we are at a crisis point in making the decision of which of those two paths we follow for genomic data."

MacArthur believes there is still time and opportunity to "get it right." Doing so, he believes, will lead to researchers learning not only about the basis of all rare diseases, but also the genetic basis of all of the different diseases that affect humanity. It will also better position drug developers to develop new therapies and physicians to better use therapeutics and lead to better ways of producing and improving health at a population level.

"We still have a chance. If we make the right decisions over the next five years we can be in a situation in 10 years' time where there are genomes and clinical data from millions of Americans and other people around the world that are available to researchers in the way that those individuals want them to be," he said. "That is, individuals who want to participate in research can make their data available. Researchers can actually get access to that data and the linkage between deep clinical records and genomic information is seamless and spans enormous sample sizes."

To share data, though, you have to have it in the first place. Recruiting patients for studies continues to be a barrier for researchers, what Anthony Philippakis, chief data officer of The Broad Institute, likes to call "data donation." "People know that you can donate your blood, you can donate your organs; we need to get into the heads of people that a lot of times what medicine needs most is their data. We need to build a culture where we're recruiting much larger numbers of people for research studies. That is a very important idea."

One place of encouragement for MacArthur is the rise of so-called "direct-to-patient research." Instead of recruiting people through medical centers for individual studies, there is growing use of online approaches to recruiting patients, running through the consent online, and providing saliva kits through the mail. He sees this as a much more scalable approach to research. All of that, he said, creates a feeling more akin to consumer technology. "You can think about the way that we are able to capture users' attention through modern software products," he said. "That same type of thinking and skillset to engage patients for research studies, I believe, is an important new tool that we have for biomedical research."

## A bigger toolkit

Walt Kowtoniuk, a principal at Third Rock Ventures, points to Genzyme's Ceredase, an enzyme replacement therapy approved in 1991 for the lysosomal storage disorder Gaucher disease, as a tipping point in the history of rare disease that showed other drugmakers it could be a viable business model to develop and market drugs for rare diseases. "What are

the major innovations? I think the big one that has really propped up the space has been drug pricing," he said. "The ability to charge a very high price per patient for these drugs. And that's what has made the financial models work out."

Though there is growing pressure on drug pricing, Kowtoniuk believes that high prices for rare disease therapies that are transformational will hold. "We're in a society where we're willing to pay for innovation and pay for value and pay for changing lives. At the same time, though, he believes that "a lot of the greed will get wrung out of the system," although he thinks regulatory action may be necessary to do so. He pointed to the example of Marathon Pharmaceuticals' deflazacort, a glucocorticoid that won FDA approval in 2017 to treat Duchenne muscular dystrophy. The steroid has long been available outside the United States, but Marathon won a lucrative priority review voucher for its efforts. When it announced plans to sell the drug at an annual price of $89,000 a year, even though the same drug was available in Canada for about $1,000 annually, it ignited a controversy. It even caused the industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA) to announce that it would reconsider its membership rules. "My view is that we want to represent companies that are really swinging for the fences… [companies] that are taking enormous risks in bringing breakthrough treatments to market," PhRMA President Stephen Ubl told *Kaiser Health News*. Marathon CEO Jeff Aronin resigned from the board of PhRMA and Marathon dropped its membership. The company sold the drug to PTC Therapeutics and wound down its business.

While Kowtoniuk believes pricing pressures will drive some price points lower in the rare disease space and may impact some investment in research and development, the critical dynamic he points to is the rise of patient groups' willingness to fund high-risk, early-stage drug discovery and translational work. That, he said, has the ability to de-risk investment in the rare disease space and change the economics of bringing these therapies to market.

"That is the riskiest capital one can deploy because the odds of reaching a viable drug are the lowest at that point. But all of a sudden, if the first million dollars into a program comes from philanthropic causes, the risk profile, and therefore the probability adjusted returns, changes dramatically," he said. "If the patient group is able to push the program all the way

**"But all of a sudden, if the first million dollars into a program comes from philanthropic causes, the risk profile, and therefore the probability adjusted returns, changes dramatically."**

*—Walt Kowtoniuk, principal at Third Rock Ventures*

to the point of initiating a clinical trial, which we've seen in some cases, that continues to shift the economic return model more and more favorably for an industry participant."

Groups like CureSMA, which provided early funding for what became the drug Spinraza, and Cystic Fibrosis Foundation, which provided early funding for the drug Kalydeco, have shown the critical role that patient groups can play in enabling the development of breakthrough medicines. While a number of patient groups have become involved in venture philanthropy to bridge funding gaps in early-stage development, others have gone so far as to start biotechnology companies themselves as a way to accelerate the development of potential therapies and ensure accessibility if they are successful at bringing them to market.

Foundation for Angelman Syndrome Therapeutics (FAST) in 2018 launched GeneTx Biotherapeutics as a for-profit company to develop and commercialize an investigational antisense drug, GTX-101, for the treatment of Angelman syndrome, a rare genetic disorder that results in development delays, impaired motor function, loss of speech, and epilepsy. It is working to develop an experimental antisense oligonucleotide that it licensed from Texas A&M University System.

"The launch of GeneTx is the logical next step in FAST's mission to cure Angelman syndrome," said Paula Evans, chairperson of FAST and CEO of GeneTx. "We want to ensure potential treatments for AS are brought to each patient as safely and expeditiously as possible and being actively involved in the interim process between bench and bedside ensures we will have a strong voice in the pricing and accessibility of possible treatments for Angelman families worldwide."

While growing scientific and financial sophistication in the patient community is accelerating this trend, there is also the evolution of new business models, such as Bridge Bio, Roivant Sciences, and the rare disease accelerator Cydan, all of which build nimble biotechs around in-licensed assets. They have shown an ability to find de-risked candidates and to efficiently move them through clinical development. But it may be that new models will need to be created to address the unique needs of rare diseases to harness the innovations of genetic medicine and deliver them to individual patients outside of the conventional drug discovery, development, and delivery model that has evolved around conditions that afflict large populations.

**New models will need to be created to address the unique needs of rare diseases.**

Chris Adams, CEO of Cydan, said it can sometimes be misleading to speak of 7,000 rare diseases, 95 percent of which are without an approved therapy. In reality, he said, there are only about 500 to 700 of these diseases where the patient population would be considered tractable and a traditional pharmaceutical might pursue a commercial opportunity in bringing a therapy to market. "If there's only a couple of dozen patients out there how are you going to justify the economic investment? Part of the models that need to be developed in the coming decade are going to be models that allow you to get to recoup your investment but not necessarily make a venture capital-like return," he said. "It's going to be hard to develop a therapy for them unless we come up with more not-for-profit-type models."

There remains work to be done to be able to deliver promising RNA-based therapeutics

**"Please don't make us still do long duration rat studies to see if it's toxic or not. Let us back off on that and do a few weeks to make sure, but not months of long extended exposure."**

*—Brad Margus, co-founder and CEO of the A-T Children's Project*

or gene therapies for any patient with any disease. But it is possible to envision having the technical ability to take vectors that have been shown safe and effective for carrying payloads to specific tissue and produce custom therapies to meet an individual patient's needs. It may be that in such cases new ways of development, manufacturing, and delivery need to be contemplated. Academic hospitals or nonprofit organizations may be better suited for delivering such therapies if a toolkit of delivery mechanisms can be tested and approved for use and specialized manufacturing centers can be enlisted to produce the needed therapies.

**Regulators will need to consider new approaches for a world where patients seek out therapies for which they will be the only recipient.**

Doing so will require regulators to consider new approaches for a world where patients may seek out therapies for which they will be the only recipient. "What does FDA do when they're faced with the question of whether they should approve a drug that can only ever benefit one patient? What does a clinical trial look like when you have a drug that can only affect one patient? How do you demonstrate safety and efficacy in those situations?" said the Broad Institute's MacArthur. "That's the kind of extreme challenges that the regulatory framework is going to face over the next few years. It needs to be resolved if we're going to be able to deliver a personalized therapy to every patient affected by rare diseases.

It's not an abstract question. It's the type of issue that's been wrestled with by the A-T Children's Project, which is focused on ataxia-telangiectasia, a rare genetic disease that attacks children, causing progressive loss of muscle control, immune system problems, and a high rate of cancer. A-T Children's Project is working to conduct a trial of an antisense oligonucleotide to treat a particular mutation in A-T. In some rare diseases, such as cystic fibrosis, the majority of patients share the same mutation. In A-T, as well as many other rare diseases, patients have different mutations. "Even though A-T is so rare—we have fewer than 500 kids in the U.S. with it—it's worse because most of the kids have different mutations," said Brad Margus, co-founder of A-T Children's Project. "If you wanted to make an antisense oligonucleotide or gene therapy approach, you have to potentially develop a separate drug for each kid."

Margus said the intent is to try it on a child to see if the strategy works. But he's also meeting with the FDA to see about ways to reduce the regulatory burden of developing such therapies when it comes to N-of-1 studies. That may require getting the FDA to think differently about what it considers a new therapy. In an antisense oligonucleotide (ASO), a vector delivers a piece of DNA. But if you use a different ASO to address a different mutation—using the same vehicle and only changing the DNA package to suit the patient's unique needs—Margus argues it's still going to the same part of their brain. Everything else is the same. "What we would like the FDA to do is treat it like a plug-and-play where the only thing we're changing is that DNA sequence," he said. "Please don't make us still do long duration rat studies to see if it's toxic or not. Let us back off on that and do a few weeks to make sure, but not months of long extended exposure. That's going to change a lot of things for rare diseases. If we can start doing trials of one here and three there."

## The price of success

Of course, all of the innovations in therapies will have little value if patients are unable to access them. A few years ago, Alastair Kent was at a patient advocacy meeting in Brussels when a woman stood up to address a

# A New Way to Make Biologics in Small Batches

Researchers at MIT have developed a way to rapidly manufacture biopharmaceuticals on demand with a small, flexible desktop system that can be easily reconfigured to make different biologics.

"Traditional biomanufacturing relies on unique processes for each new molecule that is produced," says J. Christopher Love, a professor of chemical engineering at MIT and a member of MIT's Koch Institute for Integrative Cancer Research. "We've demonstrated a single hardware configuration that can produce different recombinant proteins in a fully automated, hands-free manner."

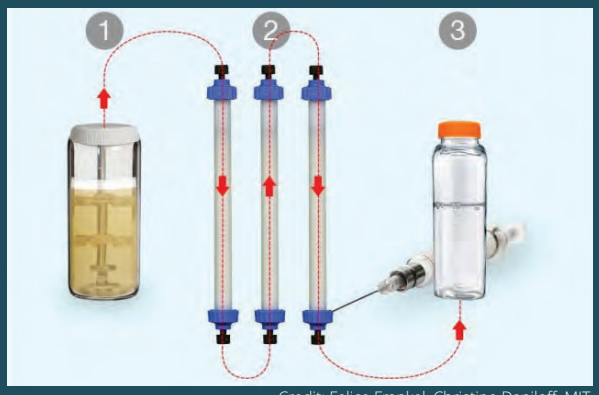
In a **letter** in an October issue of *Nature Biotechnology,* Love and his co-authors reported how they used this manufacturing system to produce three different biopharmaceuticals, and showed that they are of comparable quality to commercially available versions.

Biopharmaceuticals are usually manufactured at large facilities dedicated to a single product. The manufacturing processes are difficult to reconfigure. Because of the inflexibility of current manufacturing approaches drug producers tend to focus on drugs needed for large patient groups.

The process uses large fermentation containers known as "bioreactors" where bacteria, yeast, or mammalian cells have been programmed to produce large quantities of a therapeutic protein. To capture the protein, a process of purification is performed to isolate the desired end product. The production process is complex and requires skilled personnel to monitor and execute many steps along the way. It can take weeks to months to produce a single batch of a drug.

The system developed by MIT researchers allows for rapid manufacturing of biopharmaceuticals on demand. The system can be easily reconfigured to produce different drugs, allowing for easy switching between products as they are needed. It also has the benefit of requiring little human oversight while maintaining the high quality of protein required for use in patients.

The system has three connected modules: the bioreactor, where yeast produce the desired protein; a purification module, where the drug molecule is separated from other proteins using chromatography; and a module in which the protein drug is suspended in a buffer that preserves it until it reaches the patient.




Credit: Felice Frankel, Christine Daniloff, MIT

**MIT chemical engineers have devised a new desktop machine that can be easily reconfigured to manufacture small amounts of different biopharmaceutical drugs.**

One aspect of the MIT process is that it uses a specialized strain of yeast that secretes far fewer proteins than the microbes and cells used in traditional biomanufacturing. This simplifies the purification process.

"Our goal was to make the entire process automated, so once you set up our system, you press 'go' and then you come back a few days later and there's purified, formulated drug waiting for you," said co-author Laura Crowell.

The MIT system could be useful for producing drugs to treat rare diseases. Currently, such diseases have few treatments available, because it's not worthwhile for drug companies to devote an entire factory to producing a drug that is not widely needed. With the new MIT technology, small-scale production of such drugs could be easily achieved, and the same machine could be used to produce a wide variety of such drugs.

Another potential use is producing small quantities of drugs needed for "precision medicine," which involves giving patients with cancer or other diseases drugs that are specific to a genetic mutation or other feature of their particular disease. Many of these drugs are also needed only in small quantities.

The approach could enable the production of biotherapeutics at the point of care. It could also provide a means of producing therapies for rare diseases for patients in parts of the world where supply chain issues and the lack of manufacturing capacity complicate access to needed therapies. The system could also be deployed to speed up the process of developing and testing new drugs.

The researchers said they are working on making their device more modular and portable, as well as experimenting with producing other therapies.

**Winning regulatory approval to market a treatment doesn't mean payers will be willing to cover the cost and make it available to patients.**

reimbursement agent who was participating in a panel discussion. "I'm suffering," she said. "You must do something for me." And the reimbursement agent replied, "Everybody I deal with is suffering. Suffering itself is not enough. I need to be able to say what it is you want me to do. And, I need to be able to say that what you want me to do is not just scientifically sensible, but also makes good economic sense, given all the other demands that are pressing on my finite budget." "Getting that argument right," said Kent, "is going to be possibly as important as getting the science done."

Kent said there doesn't appear to be a single right answer to that question, but that access is the issue that everyone is struggling with as they try to find a way of generating a realistic and sustainable framework by which innovative, novel therapies become available to those who need them, on a fair, rational, and timely basis. For a company that has defied the odds and been successful at discovering and developing a rare disease therapy, winning

Alastair Kent, former executive director of Genetic Alliance UK

regulatory approval to market the treatment doesn't mean that payers will be willing to cover the cost and make it available to patients.

Adding to the challenge in both developing and developed countries are the rise of chronic diseases and aging populations that are straining healthcare systems as policymakers and payers increasingly view healthcare as a finite resource that must be used to address a broad set of competing demands. "One of the crucial issues that we have to give attention to is how the rare disease community makes its voice heard and makes an increasing clamor for healthcare support in a growing range of different contexts," said Kent. "The difficulty that we face, particularly thinking about it from a patient advocacy point of view, is generating sufficiently robust evidence to convince those people who hold the purse strings that the thing we're advocating for, in terms of bringing about improvement in the quality or quantity of our lives, provides value for money, as compared with the other things which they might want to spend that cash on."

That's a situation made all the more difficult for ultra-rare conditions that may be poorly understood, or treatments that may involve off-label use of therapies approved for other conditions. Kent argues that treatments need to be placed in a broader context, such as the cost of using a therapy versus the cost of hospitalizations that a condition may necessitate, the impact on the livelihood of other family members, the mental health costs, and broader societal impacts.

Sean Ekins, founder and CEO of Collaborations Pharmaceuticals, which works with rare disease foundations, academic scientists, and other companies as partners to develop clinical candidates for rare or neglected diseases, thinks progress in the area of rare diseases is slowed by a tendency to conduct drug discovery and development in ways that they have always been done. "We can change it," he said. "We need to make people aware that there are other ways to do things and we just have to be open to that." He doesn't believe that metrics such as the size of the patient population or market potential should be barriers to the development of needed therapies.

He said rare disease patients and their families have brought a different mindset to solving these problems, but then turn to people from the traditional pharmaceutical industry who follow processes that require a long and costly development path. "They think, 'Oh well, we can fix it because we've got a process, and that process will take 20 or 30 years to develop the drug and it will take hundreds of millions, if not

## Burden and Economic Impact of Pediatric Genetic Disease

A December 2018 **study** in *Genetics in Medicine* [Gonzaludo et al.] used the 2012 Kids' Inpatient Database for neonatal and pediatric patients discharged with a genetic disease or suspected genetic disease to calculate the cost to the U.S. healthcare system.

Number of weighted discharges: **5.85 million**

Percent of discharges that included genetic disease-associated codes: **2.6 to 14 percent**

Extent of higher cost in neonatal patients: **$16,000 to $77,000**

Extent of higher cost in pediatric patients: **$12,000 to $17,000**

Total cost of genetic disease: **$14 billion to $57 billion**

Percent of the national bill for pediatric patients in 2012: **11 percent to 46 percent**

*Source: Gonzaludo et al, Estimating the burden and economic impact of pediatric genetic disease, Genetics in Medicine December 20, 2018,* ***https://www.nature.com/articles/s41436-018-0398-5***

billions, of dollars to do it," he said. "And then I throw my hands up in the air thinking well that's not the way we have to do it. We have to think about it differently. We have to do it cheaper. We have to do it faster. I can't wait 20 or 30 years for us to fix some of these rare diseases. We have to do it in the next couple of years."

In a **correspondence** in a 2017 issue of *Nature Biotechnology,* Ekins argues the emerging field of gene therapy is evolving with competing vectors, patents, and little sharing or open collaboration. Progress is further delayed by vector manufacturing delays and a lengthy institutional review board regulatory process.[23] He said the same issues will exist for protein replacements, where there is as much art as science in the purification and expression of these therapies, and expertise is often captive within a drug company. He suggests looking to the example of Henry Ford and the production line to find ways to generalize the approach of developing therapeutics of all types. As an example, he points to gene therapy. He suggests developing the best vector and serotype to deliver a gene therapy to a particular organ and using that for tens or hundreds of diseases at the same time, rather than just one. Similarly, he said, the same approach could be used to determine the best way to make human proteins, deliver gene therapies to the brain, or scale up manufacturing for multiple protein replacement therapies. "One could imagine a factory instead of a lab, with hundreds of skilled experts working on each step of producing treatments for rare diseases with the infrastructure to retain the talent and share the knowledge in one place," he wrote.

While it is not surprising for parents to be willing to pursue a life-saving therapy for a child at any cost, as the ability to treat and cure rare disease expands, the cost implications to public healthcare systems and private insurers will become a greater issue. While a public health case can be made for the economic benefits of treating and curing patients and the societal and economic good of allowing patients and caregivers to return to productivity, the better job innovators can do to find new ways of cost-effectively diagnosing and treating rare diseases, the greater the ability to spread those economic benefits.

Although this report has been focused largely on the United States and developed world, rare disease is a global health problem that afflicts an estimated 400 million people.

**"It makes no sense to come up with 7,000 different solutions. Everything we do is identify common limitations... What we have in common outweighs the differences."**

*—Christopher Austin, director of the National Center for Advancing Translational Sciences*

People in many parts of the world are doomed to suffer and die due to their inability to access therapies that have long been available in the United States and elsewhere. While the focus on innovation has been on therapeutic modalities, innovation is needed throughout the entire discovery, development, manufacturing, and distribution process if these therapies are to benefit a global patient population in need of access to them. And, access and cost will be inextricably linked.

## Paying for value

Producers of high-priced gene therapies have been at the forefront of wrestling with the challenge of convincing payers of the value of their therapies while allowing them a way to contend with the immediate budgetary implications of having to pay for patients receiving million-dollar treatments. It's by no means a problem unique to the rare disease sector. In fact, several drugmakers with costly therapies that carry uncertain clinical benefits are experimenting with new payment models. When Novartis won approval for its gene therapy Zolgensma for the rare and fatal neuromuscular condition spinal muscular atrophy, it announced a plan to allow payers to spread the $2.1 million cost of the one-time therapy over five years and to tie payments to outcomes. Such an approach may help address some resistance to paying for therapies that may not work for all patients or may have uncertain durability. In a July /August **article** in *In Vivo* [Cook et al.], representatives of the Alliance for Regenerative Medicine, an international organization of gene and cell therapy stakeholders, argue that innovators and payers are increasingly believing that new models for reimbursement and financing these therapies will be needed.[24] "There is a growing consensus among stakeholders that reimbursement models that enable payers to make their payments over time and/or enable payment tied to the therapy performance may be appropriate for regenerative medicines as they facilitate patient access to new therapies quickly while enabling payers to manage their overall budget impact and limit risk if the therapy does not perform as expected," they wrote.

**The bigger challenge may be having physicians in place with an understanding of genetic medicine.**

## A human resources problem

In a world of dizzying scientific breakthroughs, it is often easy to overlook more mundane issues, such as human resources. In the case of rare diseases, though the genetic counselor workforce grew by 88 percent from 2006-2016, a study by the Genetic Counselor Workforce Working Group, a group of professional organizations, forecasts a shortage of genetic counselors to deliver care directly to patients over the next decade. The proliferation of genetic testing and the falling cost of whole genome sequencing promises to expand the use of these tools and expand demand for people trained to explain their meaning to patients.

Genetic counselors represent just one piece of the challenge. The bigger challenge may be having physicians in place with an understanding of genetic medicine. "It's not just the paucity of training doctors are given on genetic disease. If you're in a medical school today, you'll hit the workforce in somewhere between five and 10 years, depending on what route you take," said Stephen Kingsmore, CEO of Rady Children's Institute for Genomic Medicine. "We have a problem that this is not taught in medical schools, but we have a more urgent problem, which is that our current workforce, the neonatologists and the intensivists in pediatric

intensive care units are the current workforce. They're this generation's workforce and they are not familiar with it. We need to train next generation's workforce, but more acutely, we've got to train this generation's workforce."

Kingsmore said we not only need to train physicians to understand what this technology is and how to use it in clinical practice, but also to change the way doctors fundamentally approach diagnosing patients. Today, physicians are trained to do an exam, take a history, formulate a differential diagnosis, order a test to confirm. They repeat the process of ordering tests until they arrive at a diagnosis. "It is counterintuitive for them to think, 'I don't need to go that route anymore. I order a genome. The result comes back,'" he said.

The old medical school adage of when you hear hoofbeats think horses not zebras, an admonishment to doctors to think of the most common explanations for patients' symptoms rather than considering a rare diagnosis, is an outdated notion in an era of genetic medicine. While such guidance may have made sense in an era when the ability to diagnose and treat rare diseases were constrained by capabilities, that's no longer the case. Doctors on the frontline of care will need to better recognize when to think in terms of genetic diseases and take advantage of new diagnostic tools available to them. The incorporation of artificial intelligence into clinical practice will help to close the gap in the current capabilities of physicians and alert them when such considerations may be appropriate.

Christopher Austin, director of the National Center for Advancing Translational Sciences at the National Institutes of Health, says that half of the failure of translating science into treatments is science and the other half is social science, involving things such as human behavior, organizational behavior, and incentives. "We need to innovate in both," he said.

But the critical shapers of the future of the rare disease landscape will be the same as in the past—patients and their families—because they are the ones who need progress to occur more than anyone else. Austin says, in the end, the scientists, drug companies, academic centers, government agencies, and investors are "middle-men" who can come into work tomorrow and shift their focus away from rare disease and do just fine. "Patients can't," he said.

"It makes no sense to come up with 7,000 different solutions. Everything we do is identify common limitations, new approaches," said Austin. "What we have in common outweighs the differences. We all have needs. That has to be the focus. I hope that happens."

Austin said the biggest challenge is in getting all of the players, including the patients, to realize that they may be more productive, not only for themselves but for everybody else, by thinking more holistically—that the breakthrough in their disease may come from another disease that they have never heard of—and that moving to a system that focuses in on the connections, the similarities among the diseases rather than the differences, may be the best way to achieve success.


Chris Austin

"We have the benefit here of having a viewpoint that few others have the privilege of having. We have a view of rare disease research, everything from basic gene discovery to applications of these drugs in the community, in a much more global, holistic way," said Austin. "When we look out at the landscape, it is blindingly obvious to us that they are the same problems. We look across these problems in disease after disease and patient group after patient group. They all think that it's different. We as human beings emphasize the differences. That is the secret of our demise." ■

# FOOTNOTES


1. Shire; Rare Disease Impact Report: Insights from patients and the medical community; April 2013, https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf

2. Finkel, Marion J., et al.; Significant Drugs of Limited Commercial Value, Report of the Interagency Task Force to the Secretary of Health, Education, and Welfare; June 29, 1979; https://rarediseases.info.nih.gov/files/1979_Interagency_Task_Force_Report_on_Significant_Drugs_of_Limited_Clinical_Value.pdf

3. Dunkle, Mary, A 30-year retrospective: National Organization for Rare Disorders, the Orphan Drug Act, and the role of rare disease patient advocacy groups; Orphan Drugs: Research and Reviews; February, 17, 2014; https://doi.org/10.2147/ODRR.S41070

4. Gottlieb, Scott; Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA's comprehensive new policy approach to facilitating the development of innovative regenerative medicine products to improve human health; November 16, 2017; https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-comprehensive-new-policy-approach-facilitating

5. Damiani, Stephen; Our Journey, Mission Massimo Foundation, https://www.missionmassimo.com/ourjourney/

6. Global Genes, Accurate Diagnosis of Rare Diseases Remains Difficult Despite Strong Physician Interest, press release, February 20, 2014; https://finance.yahoo.com/news/accurate-diagnosis-rare-diseases-remains-140000027.html

7. Taft, Ryan J., et al.; Mutations in DARS Cause Hypomyelination with Brain Stem and Spinal Cord Involvement and Leg Spasticity; American Journal of Human Genetics; May 2, 2013; DOI: https://doi.org/10.1016/j.ajhg.2013.04.006

8. Scocchia, Alicia, et al.; Clinical whole genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico, Genomic Medicine, https://doi.org/10.1038/s41525-018-0076-1

9. Chong, Jessica X., et al.; The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities; The American Journal of Human Genetics, August 6, 2015; https://doi.org/10.1016/j.ajhg.2015.06.009

10. Kuilenburg, Andre B.P. van, et al.; Glutaminase Deficiency Caused by Short Tandem Repeat Expansion in GLS; The New England Journal of Medicine, April 11, 2019; DOI: https://doi.org/10.1056/NEJMoa1806627

11. Philippidis, Alex; The 100,000 Genomes Club; Genetic Engineering & Biotechnology News; September 12, 2018; https://www.genengnews.com/insights/the-100000-genomes-club/

12. Clark, Michelle M., et al.; Diagnosis of genetic diseases in seriously ill children by rapid whole-genome sequencing and automated phenotyping and interpretation, Science Translational Medicine, April 24, 2019; https://doi.org/10.1126/scitranslmed.aat6177

13. Zuccato, Mary, et al.; The Collaborative Network Approach: a model for advancing patient-centric research for Castleman disease and other rare diseases; Emerging Topics in Life Sciences; March 13, 2019; https://doi.org/10.1042/ETLS20180178

**14.** Pullen, Lara C., et al.; Cognitive Improvements in Children with Prader-Willi Syndrome Following Pitolisant Treatment—Patient Reports; The Journal of Pediatric Pharmacology and Therapeutics, March-April 2019; **https://doi.org/10.5863/1551-6776-24.2.166**

**15.** Keshavan, Meghana; Saving Mila: How a tailor-made therapy, developed in a flash, may have halted a young girl's rare disease; STAT; October 22, 2018; **https://www.statnews.com/2018/10/22/a-tailor-made-therapy-may-have-halted-a-rare-disease/**

**16.** Jayasundara, Kavisha, et al. ; Estimating the clinical cost of drug development for orphan versus non-orphan drugs; Orphanet Journal of Rare Diseases, January 10, 2019; **https://doi.org/10.1186/s13023-018-0990-4**

**17.** Fogel, David B.; Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review; Contemporary Clinical Trials Communications; September 11, 2018; **https://doi.org/10.1016/j.conctc.2018.08.001**

**18.** Willig, Laurel K., et al.; Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings; The Lancet Respiratory Medicine; May 1, 2015; **https://doi.org/10.1016/S2213-2600(15)00139-3**

**19.** Wolyniak, M., et al.; Improving medical students' knowledge of genetic disease: a review of current and emerging pedagogical practices; Advances in Medical Education and Practice; October 29, 2015; **https://doi.org/10.2147/AMEP.S73644**

**20.** Alapati, Deepthi, et al.; In utero gene editing for monogenic lung disease; Science Translational Medicine, April 17, 2019; **https://doi.org/10.1126/scitranslmed.aav8375**

**21.** Molteni, Megan; CRISPR Gene Editing is Coming for the Womb; Wired.com; April 17, 2019; **https://www.wired.com/story/crispr-gene-editing-is-coming-for-the-womb/**

**22.** Johnston, Josephine, et al.; Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies; The Hasting Center Report; August 14, 2018; **https://doi.org/10.1002/hast.874**

**23.** Ekins, Sean; Industrializing rare disease therapy discovery and development; Nature Biotechnology; February 8, 2017; **https://doi.org/10.1038/nbt.3787**

**24.** Cook, Francesca, et al.; Regenerative Medicine is Here: New Payment Models Key to Patient Access; In Vivo; July/August 2018; **https://alliancerm.org/wp-content/uploads/2018/07/ARM_WhitePaper3_IV1807_LRS.pdf**

**25.** Bastarache, Lisa et al.; Phenotype risk scores identify patients with unrecognized Mendelian disease patterns, Science; March 16, 2018 DOI: 10.1126/science.aal4043

# ACKNOWLEDGMENTS

**About the Author**
Daniel S. Levine

Daniel Levine is an award-winning business journalist who has reported on the life sciences, economic development, and business policy issues throughout his career. He serves as editor of Global Genes' RARE Daily. He is founder of Levine Media Group, host of The Bio Report and RARECast podcasts, a senior fellow at the Center for Medicine in the Public Interest, and a member of the advisory board of BioCalifornia. He co-authored A Rare Breed (2017), a history of the rare disease drug developer BioMarin Pharmaceutical, is author of a forthcoming history of Exelixis Pharmaceuticals (2019), and served as editor and lead writer of the 2011 through 2014 editions of Burrill & Company's annual report on the biotechnology industry.

**Copyeditor:** Marie Daghlian
**Graphic Design and Production:** Monica Toth

**Global Genes Project Team**
Nicole Boice
Maureen McArthur
Tiffany Leite
Rose Mary Moegling

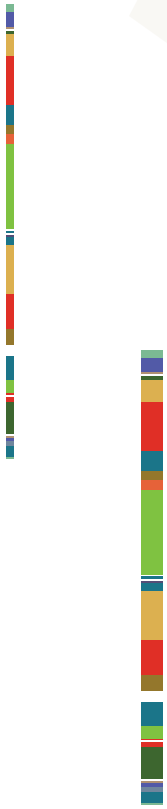
**Project advisor:** Craig Martin, CEO Rithm Health

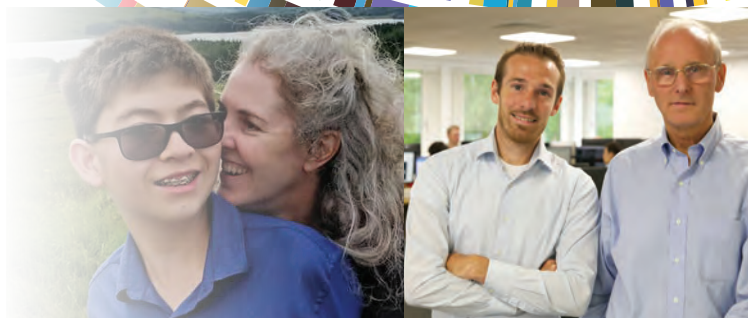
**Medical and Scientific Advisory Board Reviewers**
Lara Bloom, International Executive Director, The Ehlers-Danlos Society
Ryan Taft, Vice President, Scientific Research, Illumina
Ethan Perlstein, CEO and founder, Perlara PBC
Christina Waters, President, CEO, and Founder, RARE Science
Maureen McArthur Hart, Strategic Advisor, Global Genes

Global Genes would like to acknowledge James O'Rourke, teaching professor of management & organization at the Mendoza College of Business at the University of Notre Dame and his 10 Years Hence Series as an inspiration for this report.

We would also like to thanks James Valentine, associate at Hyman, Phelps & McNamara for his review and input.

**Global Genes would like to thank the following people who generously gave their time and shared their experiences and perspectives for this report:** Chris Adams, CEO of Cydan; Christopher Austin, Director of the National Center for Advancing Translational Sciences; Michael Bamshad, Director of Human Genetics at the University of Washington division of Genetics; David Bick, Chief Medical Officer of HudsonAlpha Institute for Biotechnology; Bo Bigelow, Chairman and Founder of Foundation for USP7-Related Diseases; George Church, Founder Nebula Genomics; Greg Cooper, faculty investigator HudsonAlpha Institute of Biotechnology; Sean Eakins, Founder and CEO of Collaborations Pharmaceuticals; David Fajgenbaum, Co-Founder and Executive Director of the Castleman Disease Collaborative Network; Onno Faber, Co-Founder and CEO of RDMD; Matthew Fox, CEO of Q-State Biosciences; Dekel Gelbman, CEO of FDNA; Chris Gibson, Co-Founder and CEO of Recursion Pharmaceuticals; Stephen Groft, Senior Advisor to the Director, National Center for Advancing Translational Sciences; Tim Guilliams, Co-Founder and CEO of Healx; Matthew Holt, Co-Chairman of Health 2.0; Alastair Kent, Former Executive Director of Genetic Alliance UK; Stephen Kingsmore, President and CEO of Rady Children's Institute for Genomic Medicine; Walt Kowtoniuk, Principal at Third Rock Ventures; David Lapidus, President of LapidusData; Daniel MacArthur, Co-Director of Medical and Population Genetics at the Broad Institute of Harvard and MIT; Christine McSherry, Co-Founder and CEO of Casimir Trials; Beth McGinn, Co-Founder and Executive Director of A Cure for Ellie; Brad Margus, Co-Founder and CEO of the A-T Children's Project; Matt Might, Director of the Hugh Kaul Personalized Medicine Institute at the University of Alabama Birmingham; Emily Milligan, Executive Director of Barth Syndrome Foundation; Anthony Philippakis, Chief Data Officer of the Broad Institute of MIT and Harvard; Maria Picone, Founder and CEO of TREND Community; Lara Pullen, Co-Founder of Chion Foundation; Kelly Ranallo, Founder and President of the Turner Syndrome Global Alliance; Kari Luther Rosbeck, President and CEO of the Tuberous Sclerosis Alliance; Morrie Ruffin, Co-Founder and Senior Advisor to the Alliance for Regenerative Medicine; Sandra Shpilberg, Founder and CEO of Seeker Health by EVERSANA; Gina Szajnuk, Co-Founder and Executive Director of the Rare and Undiagnosed Network; Ryan Taft, Vice President of Scientific Research at Illumina; Sharon Terry, CEO at Genetic Alliance; Sue Washer, President and CEO at AGTC; John Wilbanks, Chief Commons Officer at Sage Bionetworks.





Global Genes®
Allies in Rare Disease

globalgenes.org • 28 Argonaut, Ste. 150, Aliso Viejo, CA 92656