NEXT 2023

The Rise of the Impatient Advocate

Global Genes®
Allies in Rare Disease

NEXT 2023

The Rise of the Impatient Advocate

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Charlene Son Rigby, CEO
Global Genes

A Letter From the CEO

Despite the financial turbulence that characterized the biotechnology sector in 2022, it was a year that saw five gene therapies—three in the United States, and two in Europe—win regulatory approvals. That was a visible reflection of the innovation that is transforming the lives of people diagnosed with a rare disease.

The growing sophistication among rare disease patient advocates about the drug development process, along with emerging technologies from genetic medicine to artificial intelligence, is giving unparalleled power to patient advocates to change the destiny for themselves and others. Rather than being passive observers who must hope that researchers and drug companies will develop needed treatments, they are taking an active role, improving the understanding of rare diseases, accelerating the diagnostic process, and driving research and development into new therapies.

As Global Genes begins the new year with an expanded focus on enabling next-generation patient advocates, following its merger with the data-sharing platform RARE-X, it is fitting that this year's NEXT report continues to highlight this trend of patients playing a central role in advancing research and development for rare disease therapies.

The challenging financial environment and technological advances are creating both greater opportunities and need for patient advocates to leverage their resources and collaborate with researchers, drug developers, and other stakeholders to provide capital, data, and perspective. And, when others are unwilling or unable to move with adequate speed, finding ways to drive progress forward.

The pace of innovation continues to accelerate. Ten years ago, it was difficult to think of sequencing a whole genome for $100, a therapy produced for a single patient, or the availability of cures for genetic diseases.

We are only constrained by the limits of our ability to imagine what is possible.

Charlene Son Rigby
CEO
Global Genes

Introduction

Acting as a Member of a Global Community

"It's truly a credit to these family organizations, who stand united across the world. It's not a political statement, it's just that they have children who are suffering, and they want to help."

—Jeremy Levin, CEO of Ovid Therapeutics on the rare disease community response to the needs of rare disease patients in Ukraine

On February 27, 2022, three days after Russia invaded Ukraine, KIF1A Chairman and Founder Luke Rosen received a message from a Ukrainian woman named Olga through his organization's Facebook page. Olga and her son Illja had been in a car for 36 hours and were trying to cross the border with Poland hoping to enter at Budomierz, a city about 50 miles from the Ukrainian city Lviv. Illja has the rare neurological condition KIF1A syndrome and was running out of antiseizure medicine.

Olga was fearful because of the dangers of suddenly stopping the medication and concerned that she would not be able to get her son needed drugs and care in time as they were stuck in traffic that was backed up for several miles from the entry into Poland as a flood of other people also sought to flee the country. There was no one from the Red Cross or other agencies who could be found, and she felt she could not abandon her car.

Rosen found his way to Adrian Goretzki, an attorney in Poland and founder and president of the Polish rare disease patient advocacy organization Healthcare Education Institute. Goretzki asked for a description of Olga's car and asked whether they could flag it in some way. Rosen thought about what they might have with them and instructed Olga to hang a sock from her rear-view mirror to help make her red Honda easy to identify. Goretzki would arrange to have paperwork ready at the border and meet Olga to expedite her crossing, but Rosen still had to figure out how to get her there.

After the Pandemic

By many measures, 2022 was a difficult year. A brutal war in Ukraine, rising food and gas prices, and turbulent capital markets set just part of the backdrop as the COVID-19 pandemic receded. For rare disease drug developers, the easy access to capital that had characterized recent years had dried up. The sell-off in biotech stocks that began in late 2021 accelerated in 2022. Companies that suffered clinical setbacks quickly moved to cut staff, pare

back programs, and conserve cash. Congress added to the woes as it considered legislation that threatened to extend the time and cost of developing many rare disease drugs.

The effects of the war in Ukraine would reverberate globally, but it would also mobilize rare disease patient advocates around the world who recognized that despite the gulfs of language, culture, and geography that might exist, as many as 2 million members of their community were caught in the war and needed help.

"Now, more than ever, we need a coordinated, holistic approach to rare disease to meet the challenges of today and the years to come."

— Yann Le Cam

When Rosen had asked Olga to describe where she was, she explained that there was one lane where vehicles moved freely. She said that lane appeared to include official vehicles and black vans. Rosen realized that there must have been other rare disease patients like Olga and her son who were stuck in the long lines at the border and that it wasn't only KIF1A families who needed help. He knew, as with Illja, there would be people running out of essential medication and who would need access to medical care. Time was working against them.

Rosen, who had been an actor prior to becoming a rare disease patient advocate, recognized the black vans Olga had seen as production vehicles. He assumed that they were allowed to pass more easily because they were film crews documenting the emerging war. He reached out to his agent and asked for a list of production companies operating near the Poland-Ukraine border and discovered he knew a sound man within one of the crews in Poland. He offered to send $5,000 via Venmo to enlist their help. Remembering the Polish patient advocate Goretzki's request to flag Olga's car in some way, Rosen thought about what people might have with them. He posted a note on social media to tell other people stuck at the border with medically complex children in need of help to hang a sock from their rear-view mirrors. He quickly raised money to pay the crew to go across the border and for the next 48 hours, they helped ferry rare disease children and their families into Poland.

Rosen, who is also senior vice president of accelerated development and community engagement at Ovid Therapeutics, realized a more sustained effort would be needed to meet the needs of rare disease patients fleeing Ukraine, as well as those who remained behind. He reached out to Ovid CEO Jeremy Levin, as well as Amicus Therapeutics CEO John Crowley. The two CEOs also joined with Craig Martin, then interim CEO of Global Genes (publisher of this report) to develop a more coordinated effort. They provided funding to Goretzki's Healthcare Education Institute, as well as other rare disease organizations and families. They also reached out to other rare disease drug companies to join the effort and provide resources to assist children and families with rare diseases attempting to flee Ukraine. More than a dozen other companies joined that effort, which provided funding to organizations providing direct or indirect aid to Ukraine, as well as rare families with tangible needs.

Ovid's Levin had already been active in working with other CEOs to respond to the Russian invasion and the growing crisis in Ukraine. On the night of the invasion, with a group of other life sciences executives, he organized a call for companies to economically disengage from Russia. More than 900 life sciences executives pledged to cease investment in Russian companies or make new investment within Russia's borders, reject investment from Russian funds, and halt collaboration or service agreements with Russian companies.[1] Working with others, Levin helped get patients across the border to Poland, arrange for care at European hospitals, and bring needed medicines into Ukraine. While many had expected a short conflict, those hopes faded as the war dragged on and the indiscriminate brutality of the attacks from intransigent Russian forces grew.

"The disruption to medical services has been so extreme that even basics such as intravenous fluids, antibiotics, bandages, and anesthetics are in short supply. Worse yet, the facilities to do intubation and to keep people on ventilators, all of these things are disrupted by Russia. And in those circumstances, the choices that are being made medically are dramatic and sad," said Levin. "I anticipate that the rare disorder community, while loved and cherished by those families, may well be put into second

place behind treating soldiers and civilians injured by the actions of the Russians, because their lives need to go on if they're going to create and continue to have a society."

While many people with rare diseases and their families fled the country, others were unable to do so. As the war escalated, missiles targeted civilian neighborhoods, schools, and hospitals, complicating not only the ability for people with rare diseases to get access to drugs and needed care, but basic necessities as well. Patient organizations in Ukraine, Europe, and the rest of the world moved with speed to respond to urgent needs from rare disease patients both leaving Ukraine and remaining there.

The European rare disease organization Eurordis worked to address the needs of Ukrainians with rare diseases. It called on its network of organizations throughout the world to help. Eurordis established a Ukraine taskforce, created an online resource center for patients and patient organizations seeking to help people, raised funds, and referred individual patients to organizations that might be able to address specific requests. As part of its efforts, Eurordis worked with the nonprofit Airbnb.org to offer people with rare diseases fleeing Ukraine temporary housing in other countries.

As the worsening humanitarian crisis unfolded, the United Nations reported that more than 12 million people in Ukraine fled their homes, more than 5 million of whom fled to neighboring countries. Coming on the heels of the COVID-19 pandemic, Eurordis said the limited capacities of countries receiving people from Ukraine raised questions about the resilience of European healthcare systems.

"The EU has a chance to change the narrative that it cannot afford to miss by leveraging its resources and increasing investment in cross-border healthcare infrastructures to address the needs of the rare disease community," said Yann Le Cam, Eurordis CEO in March 2022 while discussing his organization's response to the crisis. "Now, more than ever, we need a coordinated, holistic approach to rare diseases to meet the challenges of today and the years to come."

An Exit Strategy

Organizations large and small felt compelled to help in whatever way they could. As soon as the war in Ukraine began, Nicole Johnson, co-founder and executive director of the International FOXG1 Foundation, checked to see if the organization had any FOXG1 families there. FOXG1 is a rare, pediatric, neurological disorder that impacts brain development and causes severe physical and cognitive disabilities. One of the hallmarks of the condition is intractable seizures.

Johnson identified Elena and her family outside of Kiev. They were unable to leave and had been living in their basement for shelter when sirens sounded. The family included Elena, her husband, her mother, her six-month-old baby, and her 3-year-old daughter Eva who had FOXG1. Eva was running out of anti-seizure medicine. Johnson reached out to another FOXG1 family in Poland, who agreed to take in the Ukrainian family, but Johnson still had to figure out how to get them there. "It was devastating to watch people try to escape getting shot at. It wasn't safe," she said. "I put feelers out there to everybody I knew to tell them this is happening, and I need help to evacuate them."

As she began searching for a solution she came across Project Dynamo, an organization that includes a veterans' coalition that helps at-risk individuals escape from war-torn areas and transports them to a safe, temporary location. The group launched a Ukraine evacuation

The first group of Ukrainian children with cancer arrive at St. Jude Children's Research Hospital in Memphis, Tennessee.

request page. With the child running out of medication, they showed up with two ambulances and over the course of three days drove them to the family in Poland. Johnson launched a support fund to help the family resettle. The family is now settled in Poland.

For other organizations, the war in Ukraine sparked large and long-term efforts. By late March, less than a month into the conflict, the first four children with cancer and their families arrived at St. Jude's in Memphis from Krakow, Poland. The children, who ranged in age from 20 months to eight years, received cancer treatments, as well as therapy to address psychological, social, emotional, and cultural needs. The children came through SAFER Ukraine, a humanitarian effort the hospital's St. Jude Global program launched following the Russian invasion. The Memphis-based research hospital, the only National Cancer Institute-designated Comprehensive Cancer Center devoted solely to children, worked with Fundacja Herosi in Poland, the Tabletochki Charity Foundation in Ukraine, Polish Society of Pediatric Oncology and Hematology, and other foundations and international organizations to evacuate children with cancer from the war zone and provide them access to medical care.

The St. Jude Global SAFER Ukraine collaborative has assisted hundreds of patients by translating medical records, coordinating transportation from Ukraine to the Unicorn Marian Wilemski Clinic in Poland for evaluation, and transporting these children to a network of cancer centers in Europe, Canada, and the United States. The Unicorn clinic, which at one time was a hotel, can accommodate up to 300 patients and family members. To minimize disruption to the lives of these children and their families, the group has sought to keep them as close to home as possible, but other factors, such as available clinical space and the specific medical needs of the patients could necessitate sending children further away.

In March 2022, a group of children with cancer, who were evacuated from war-torn Ukraine, arrive in Memphis, Tennessee to resume treatment.

Everything Changed

In Poland, which received the largest number of Ukrainian refugees, Healthcare Education Fund's Goretzki said the need in neighboring Ukraine transformed the organization's priorities overnight and he expected that the need would remain well beyond the conflict. Goretzki placed the organization's regular day-to-day projects on hold to focus on helping Ukrainian patients.

The Healthcare Education Fund had a history of working with rare disease patients in Ukraine before the start of the war. Goretzki said the level of care for people with rare diseases in Ukraine was significantly lower than in other European Union countries. He said Ukrainians who fled their homes for countries in the European Union have had a chance to receive better treatment. "But believe me," he said, "most of them would like to go back to their homeland than to even have better treatment in a totally different country."

The organization said what started as an ad hoc project has become a well thought out support system with a dedicated team. It organizes the transportation of medicines and medical equipment to hospitals in Ukraine that are treating rare disease patients. For patients in Ukraine looking to get out of the country, it assists with transportation and prepares legal documentation to expedite the process of getting them across the border to bypass waits that could range from hours to days. It connects these people with physicians, housing, transportation, and translation services. It also takes steps to ensure that patients receiving specific treatments can continue doing so as fast as possible after reaching Poland.

Emily, an infant who had severe combined immunodeficiency or SCID had been scheduled for a life-saving bone marrow transplant in Kiev. The condition, also known as bubble boy disease, is caused by mutations in genes that give rise to the infection fighting portions of the immune system. Without treatment to restore the immune system, children usually die within the first two years of life. The hospital that was readying to do her procedure closed after the Russian military began bombing the city. Even though a donor had been secured, the operation was canceled and the family was told there would be no procedures. The Healthcare Education Fund found a hospital in Poland that was willing to do the procedure in less than 24 hours after her family reached out to them. In all, the organization had helped four patients receive bone marrow transplants and two receive liver transplants.

Patients Without Borders

Ovid Therapeutics CEO Levin said that rare disease patient communities are global, and the Internet has enabled communication across borders between patients and their families. "What that has provided is the knowledge that a family in Romania will know a family in Rhode Island, a family in Ukraine will know a family in Utah," he said. As the invasion caused outrage from many nations in response, it also activated many people in the rare disease to community to try to meet the needs of people with rare diseases and their families.

Levin said what's remarkable about the rare disease community is that they live their disorder every day of their lives. They share experiences when there are no treatments. They learn from others around the world. When there is a treatment, they want to share it with those who they most care for around the world. And when there isn't, they learn the name of the family, the father, the mother, the child, then offer them their ideas. Will they eat something new? Does giving them a different kind of diet have an impact on the disorder?

"What it says about it is that the disorder crosses boundaries and the commitment crosses boundaries irrespective of the political situation, irrespective of the nationality, irrespective of the economic stance of individuals," said Levin. "And it's truly a credit to these family organizations, who stand united across the world. It's not a political statement, it's just that they have children who are suffering, and they want to help." ■

"But believe me, most of them would like to go back to their homeland than to even have better treatment in a totally different country."

—Adrian Goretzki

Seize the Data

"These patient-driven studies are not a fad or one-offs. This is what's going to fundamentally change how we can move the needle on some of these rare conditions."

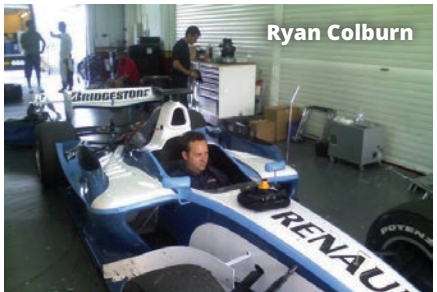
— Farid Vij, president and general manager of data for Invitae

Ryan Colburn has worked as an engineer on race cars and rockets. He has a natural curiosity that gets expressed in his penchant to take things apart to see how they work and what can be done to make them better.

In 2015, Colburn was diagnosed at the age of 31 with late onset Pompe disease, a lysosomal storage disorder in which an enzyme deficiency results in an accumulation of a complex sugar in the cells of the body and causes damage to muscles, the heart, and other organs.

Pompe disease was first identified in 1932 and the first treatment for the condition, an enzyme replacement therapy, won U.S. Food and Drug Administration approval in 2006. In the world of rare diseases, it's got the benefit of being well characterized, a well-established patient community, and available therapies with more in development.

What Colburn started to take apart and tinker with a few years ago wasn't a Formula 1 brake assembly, but the incidence rate for Pompe disease. He grew frustrated when he realized that the widely used incidence rate of 1 in 40,000 for Pompe disease was based on two small studies more than 20 years old that didn't factor in all that had been learned since that time. Even though there was significantly more data to analyze, nobody had made any real effort to develop a more accurate figure. And that, he said, has consequences.



"Being more common than that is an attractive thing for creating business cases, for increased study, and basic understanding that can impact the way that we do development," he said. "I was 31 when I was diagnosed but had symptoms since childhood and maybe birth, and I wasn't alone. How many other people out there are undiagnosed but could benefit from being on treatment? How much could the overall rate at which we are developing knowledge benefit from giving those additional people an opportunity to participate?"

The challenge of accelerating the diagnosis of people with rare diseases and the development of treatments is often complicated by the small patient populations for these conditions that constrain the gathering of adequate amounts of data to understand them. In reality, data exists all around us. One challenge is finding where data already exists, freeing it from where it may be

locked away, and putting it to work to answer questions that can advance an understanding of rare diseases. Overcoming these data silos is essential at every stage of the rare disease continuum from the basic understanding of a rare disease to refining how physicians can best treat a given patient.

Counting the Diagnosed

Colburn took it upon himself to determine a more accurate incidence rate for Pompe disease by gathering data from available newborn screening tests. Though there is an organization in the United States that collects and maintains all of the states' newborn test data, it refused to share it with him. Instead he contacted the department within each state to get the data directly from them. That took some persistence, but he prevailed. He also obtained newborn screening data from Taiwan, which had screened more than 1.3 million newborns for Pompe. Instead of extrapolating an incidence rate from a small sample, Colburn was able to determine the incidence rate based on the results of 11.6 million tests. He determined the actual incidence rate for Pompe disease among those 11.6 million tests is 1 in 18,711, more than twice the commonly used rate for the condition. He is working on publishing his results in a scientific journal.

He said the newborn screening data, which represents an actual count, can test the quality of an analysis using publicly available data, and can be used to generate new understanding of Pompe and other genetic diseases. Colburn noted that a researcher in Korea recently published a study using publicly available genetic data, which included more than 141,000 genome and exome sequences that were cross checked with a set of known variants for Pompe disease to get an estimate of 1 in 23,000.

"That analysis was done using, for the most part, wholly available data that anybody can use to analyze a given condition as long as they have some knowledge of what the genetic basis is for that condition," said Colburn. "By comparing her math to our math, with our math at this point serving as a reference of truth because it's a direct calculation using a direct detection method for the condition, we can compare how close this publicly available estimate is to the truth. And, in doing so, we can validate the goodness of that publicly available data for other conditions."

Colburn estimates that only about 3 percent of people with Pompe disease have their diagnosis. He believes that some of that is due to the severe infantile form being particularly devastating if not treated immediately, and as a result being lost before diagnosis, as well as significant portions of the mid-mild portion of the Pompe spectrum being under or mis-diagnosed. He's hoping to use this data alongside the work of others, to convince pharmaceutical companies and public health programs to address the gap in diagnosis. Beyond that, while resetting the understanding of Pompe, he's trying to carve a strategic path for others to develop more accurate incidence rates for other rare diseases.

Accelerating the Move to the Clinic

While many researchers and drug developers bemoan the lack of available data about given rare diseases. One frustration is that there is often data that exists, but it is kept out of reach. Nevertheless, advocates, researchers, and drug developers are finding ways to use existing data to do more than just calculate the incidence rates for a rare disease. These efforts show how people can leverage technology and existing real-world data to change the understanding of a disease, speed the development of therapies, and improve existing treatments.

Consider Praxis Precision Medicines, which is developing an antisense oligonucleotide to treat children with early-onset SCN2A developmental and epileptic encephalopathy (DEE). By targeting the underlying cause of early-seizure-onset SCN2A-DEE, Praxis hopes to treat seizures and other symptoms in patients with

"How many other people out there are undiagnosed but could benefit from being on treatment?"

— Ryan Colburn

gain-of-function SCN2A mutations. As part of its application to the U.S. Food and Drug Administration to begin human clinical trials of its experimental therapy PRAX-222, an ASO designed to selectively decrease SCN2A gene expression, the company submitted a natural history drawn from clinical data by Invitae's Ciitizen platform. The agency cleared the application in September 2022. It is believed to be the first instance where a natural history study drawn from real-world evidence had been accepted by regulators as part of an application to begin human clinical studies.

"If we were to design a clinical trial today with the knowledge that we have, without looking at these types of databases, we might design a trial that would never enroll."

—Brian Pfister

For many rare conditions, natural history studies do not exist to document the disease burden and unmet medical need. In addition, the usual method of collecting these data by having patients seen across a number of geographically dispersed sites, is cost-intensive, time-consuming, and ill-suited for the participation of people with rare diseases. With its Ciitizen platform, Invitae was able to take ten years of data and amass a natural history in just six months. In doing so, it overlaid genetic data and EEG results as part of its work. And while natural history studies can be demanding on patients, some of whom may drop out of a study as their condition progresses, Invitae does the heavy lifting by gathering all of the data from the various providers who cared for a given patient.

Praxis turned to Invitae's Ciitizen platform, which can rapidly collect and analyze medical history data to support an understanding of the patient population and disease severity. The data can be used as natural history data for regulatory submissions, and can inform protocol design, and inclusion and exclusion criteria for clinical studies.

"This does break open the door on the regulatory side. It is something that the FDA is more than open-minded to. They've given a green light and I think there's a lot more coming after that," said Farid Vij, president and general manager of data for Invitae. "We fool ourselves thinking we can continue to do the traditional, population-level way that we've done it in the past. These patient-driven studies are not a fad or one-offs. This is what's going to fundamentally change how we can move the needle on some of these rare conditions."

The data, collected on behalf of SCN2A-DEE patients, is de-identified and shared with the consent of the patient. The companies said it represents the richest aggregation of real-world clinical evidence for SCN2A-DEE patients. The data generated by Invitae's Ciitizen platform is comprehensive, leveraging the HIPAA right of access to gather full medical records, longitudinally, from all of the patients' sites of care. Under Invitae's data collection and sharing model, patients, patient advocacy groups, and researchers can all access the underlying data for the SCN2A-DEE natural history study. Patients have complete access to their records for their own use and are also able to stay informed about the research throughout the study.

The companies said the approach addresses many of the limitations of other data sources FDA previously raised in draft guidance on the use of real-word data to support regulatory submissions, such as de-identified provider electronic medical records and claims data. Invitae's approach, they said, also addresses many of the logistical, financial, and methodological limitations of the site-based natural history studies by rapidly enrolling a diverse and representative sample of patients directly without the need to work with sites on recruitment and data collection.

Brian Pfister, vice president of global medical affairs for Praxis, said the Ciitizen data offers many advantages over a conventional natural history beyond speed and cost. He noted that

if new research questions arise, the existing data set can be queried for them at relatively little expense or effort rather than having to amend the study protocol, contact every patient caregiver, and have them complete a new questionnaire. It's also far less burdensome to patients, who he said sometimes suffer from a "parking lot effect," a term used to describe people who hastily fill out documents in the parking lot of a physician's office because they hadn't found time to do it leisurely. It also provides a better sense of the progression of a disease to allow researchers to be thoughtful about clinical trial design and patient enrollment.

"With this approach you get a better feel for things from a clinical trial standpoint. If we were to design a clinical trial today with the knowledge that we have, without looking at these type of databases, we might design a trial that would never enroll," said Pfister. "The amount of delayed time to try to get it right is astronomical in these developmental epileptic encephalopathies. Now I can figure out this inclusion criteria is going to cause me trouble, and of the X number of patients I look at, none of them qualify based upon this. Then I can go back and we can run these virtual discussions and virtual clinical trials ahead of time and figure out where it's going to land."

Leveraging Failure

One place where troves of data that may provide valuable insights into rare diseases that is largely untapped is in biopharmaceutical companies that have programs that failed. Though there are examples of biopharmaceutical companies sharing this data with others in the hopes of advancing knowledge, such instances still are not yet the norm.

In April 2021, Ovid Therapeutics reported it would discontinue development of OV101, an experimental therapy to treat Angelman syndrome. Angelman syndrome is a rare genetic condition that is characterized by delayed development, intellectual disability, severe speech impairment, problems with movement and balance, seizures, sleep disorders, and anxiety.

That decision followed news in December of 2020 that the experimental therapy, which targets receptors believed to play a central role in the physiological process in the brain underlying certain neurodevelopmental disorders, failed to achieve its primary endpoint in a late-stage study dubbed NEPTUNE. Ovid is still pursuing an earlier-stage RNA therapy to treat Angelman, which targets the underlying genetic cause of the disease. But rather than just put its data on a shelf, in September 2022 the company donated data from the program to the Angelman Syndrome Foundation.

"Our view was, given the enormous collaboration that we'd had with the community and that we had likely the largest compilation of baseline data in Angelman syndrome, we felt it was our responsibility to donate," said Jeremy Levin, CEO of Ovid Therapeutics. "This is one way when you're not successful in a clinical trial, that you can then move forward to take the learnings you have from that clinical trial. Although the molecule may not have been successful, the trial itself harvested an enormous amount of information and that could potentially help break open the disorder. What we hope by donating this data is that the scientists will use it to begin to paint a much more sophisticated picture of the condition and its progression."

Ovid agreed to provide baseline data from NEPTUNE, one of the largest clinical development programs conducted within Angelman syndrome. The data will be added to Angelman Syndrome Foundation's Linking Angelman and Dup15q Data for Expanded Research (LADDER) database. The database houses data on individuals with Angelman or Dup15q syndromes collected from multiple sources, such as research studies, registries, caregiver reports, and clinic visits. The goal is to link these disparate sources of information through LADDER to advance research and accelerate the development of treatments for individuals with Angelman or Dup15q.

"This is a beautiful example of how industry and patient advocacy organizations can and should work together," said Amanda Moore, CEO of the Angelman Syndrome Foundation. "I get how

"This is a beautiful example of how industry and patient advocacy organizations can and should work together."

—Amanda Moore

Count Me In Launches Rare Cancer Research Projects

Rare Daily Staff

Count Me In, a non-profit cancer research initiative, is inviting patients living with the rare cancer leiomyosarcoma to share their data and become partners in research to drive new discoveries and improve understanding of this rare cancer.

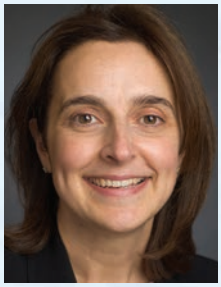
The Leiomyosarcoma Project joins the Osteosarcoma Project, another patient-partnered rare cancer research initiative offered through Count Me In that seeks to accelerate the pace of cancer research by allowing patients to easily share their health data. Federal funding from the Cancer Moonshot, as part of the Participant Engagement and Cancer Genome Sequencing Network, is supporting both projects.

Current therapies for rare cancers are limited, which makes the availability of patient data crucial for conditions such as leiomyosarcoma and osteosarcoma.

Leiomyosarcoma is a smooth muscle soft tissue sarcoma that can arise from almost any site in the body. Osteosarcoma is a rare bone cancer that primarily impacts adolescents and young adults ages 10 to 30.

Approximately 3,000 new patients are diagnosed with osteosarcoma or leiomyosarcoma in the United States each year. While the cancers are different, treatment options have not substantially progressed over the last 40 years. By providing researchers with patients' data, Count Me In aims to drive a new understanding of these diseases and unlock future therapies.

Count Me In engages cancer patients in the United States and Canada. Through the projects, participants share their medical records, biological samples, and personal cancer experiences. Count Me In then analyzes this data and generates databases of clinical, genomic, molecular, and patient-reported data that can be easily accessed by scientific and medical communities worldwide.

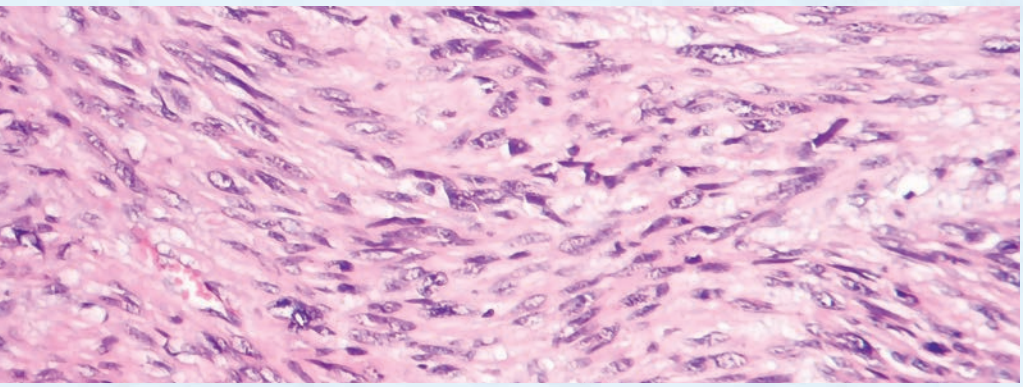


"Bringing together patients, data, and the sarcoma provider community will create some of the largest genomic datasets ever to exist in these rare, and often stubborn tumors."

—Suzanne George

"Bringing together patients, data, and the sarcoma provider community will create some of the largest genomic datasets ever to exist in these rare, and often stubborn tumors," said Suzanne George, clinical research director of the Sarcoma Center at Dana-Farber Cancer Institute and a clinical champion of the Leiomyosarcoma Project for Count Me In. She said Count Me In will share research learnings with patients directly as the project generates new data.

Patients can self-enroll through the projects' online portals. Once enrolled, they will be asked to provide saliva or blood samples and can share their health information with researchers. Count Me In is studying additional cancer types with existing patient-partnered research projects that are focused on metastatic breast cancer, angiosarcoma, metastatic prostate cancer, esophageal and stomach cancer, primary brain tumors, colorectal cancer, and others.



"You do not have to be a philanthropist or even a researcher to contribute greatly to osteosarcoma research," said Ann Graham, an osteosarcoma survivor and executive director of MIB Agents, a leading pediatric osteosarcoma nonprofit organization. "With the Osteosarcoma Project, it is fast, simple, and free to affect change for osteosarcoma."

much money industry puts into getting this data, but to set the tone for the Angelman community that Ovid has set, to say, 'We invested a lot into this program and we care so much about the Angelman community that we are going to give this data back so you can use it to continue the hard work and the fight that you're doing to find treatments for your individuals with Angelman syndrome.' My hope is that all of the other industry that are in the space can see the importance of this to our community and the beautiful gift they have the power to give back to the community in order for us to get to that finish line."

Treating with Precision

While some organizations are harnessing existing data to improve the understanding of rare diseases or to aid in the development of new treatments, others are using data to improve outcomes for patients by taking a precision medicine approach to matching the right therapy to the right patient.

Though advances have been made in the treatment of the rare blood cancer multiple myeloma, fundamental questions about how to optimize therapies for individual patients remain. The Multiple Myeloma Research Foundation launched CureCloud, an initiative to gather detailed genomic and health data from thousands of patients to both bring a precision medicine approach to the treatment of multiple myeloma and fuel the development of new breakthroughs.

Multiple myeloma is a rare blood cancer that affects the plasma cells and there are about 140,000 patients in the United States. In multiple myeloma malignant plasma cells start to accumulate in the bone marrow and produce the abnormal M protein. Patients with the condition begin to develop anemia and suffer bone damage, impaired immune function, and organ damage as the disease progresses.

There have been significant advancements in the treatment of patients with multiple myeloma. Despite a growing arsenal that includes stem cell transplants, immunomodulatory drugs, proteasome inhibitors, steroids, and immunotherapy agents including CAR T cell therapy, the overall five-year survival rate is still only about 55 percent for people with disease. In the United States, about 12,000 die from multiple myeloma every year.

Michael Andreini, president and CEO of the Multiple Myeloma Research Foundation, said the CureCloud initiative is gathering patient data with the hope of transforming the treatment of multiple myeloma with precision medicine.

"There still is a fundamental question about how can we optimize these treatments for every patient given their unique disease characteristics and stage of disease? That, to us, is essentially a precision medicine-based question," he said. "What are the right combinations and sequencing approaches of these treatments? When should we give these treatments to patients and for which patients? Ultimately, the goal is to make sure that all patients maximize the efficacy from all the available agents for them."

The CureCloud is a direct-to-patient registry platform that's capturing longitudinal genomic data from a targeted gene panel using peripheral blood samples and clinical data from electronic health record information. The work is being done in a clinical grade environment so the organization can return results from genomic testing back to patients and their treating clinicians to inform their overall care. CureCloud matches patients to potential clinical trials associated with the genomic alterations or identified through the test.

"We think bringing those two pieces of data together are going to be helpful in informing the next era of precision medicine breakthroughs that's going to help us identify new targets for drug discovery, and new biomarkers to inform care," said Andreini. "Ultimately the idea is to help inform care pathways overall to make sure that patients are having the best possible options given this broad armamentarium for their treatment."

MMRF is planning to add patient-reported outcomes data to the overall study to better

"Ultimately the idea is to help inform care pathways overall to make sure that patients are having the best possible options given this broad armamentarium for their treatment."

— Michael Andreini

understand the individual patient journey and how they're feeling given certain treatments and where they are in their overall journey.

One advantage Andreini sees to the CureCloud is that it is operated by a nonprofit, patient-centered research organization. He believes such an organization has a unique role to play since they are free of the profit constraints of industry and grant requirements of academia. "These types of organizations are maybe unique in having more access to patients than any other research institution and can more freely share the data with other researchers," he said. "Data is fractured and in lots of different silos. We think having larger, more robust data sets that can be accessed by more researchers is important to driving progress."

Changing Mindsets to Share Datasets

A world of potentially useful data for advancing the development of therapies remains siloed in universities, hospitals, and biopharmaceutical companies. Karmen Trzupek, senior director of scientific programs for RARE-X, the collaborative platform for global sharing of rare disease patient data, said the biggest obstacle is an outdated paradigm built on a belief that data is most useful if I own it, and by owning it, I ensure that others can't have access to it. "That's the model we have to break," she said. RARE-X merged with Global Genes, the publisher of the NEXT report, at the end of 2022.

"I don't think we can understate the opportunity from data that already exists."

— Karmen Trzupek

"I don't think we can understate the opportunity from data that already exists. From RARE-X's perspective, this is such a huge part of why we're here and the work that we're trying to do," said Trzupek. "We have these two platforms. We have that data collection platform for new data, but then we have this platform through the Broad Institute, Terra, to pull together existing data sets and align them so that we generate this massive body of data in rare diseases that currently just doesn't exist."

Trzupek believes the growing sophistication that rare disease patients have about data is starting to change the way data holders think. Data holders are also starting to recognize that they alone don't have the resources needed to continue to strengthen and grow their data. By sharing it with others, they are finding they can leverage what they have and also share the cost of collecting and maintaining that data.

Trzupek is heading a RARE-X led data consortium focused on rare genetic disorders primarily affecting vision in conjunction with a group of patient advocacy organizations. They are pulling data from various sources to make it available through a central point. This includes patient registries, imaging studies, and clinical research data. In some cases, researchers were happy to share their data, but lacked the infrastructure and resources to do so. The RARE-X effort solves that problem by taking that responsibility from data owners and doing it for them. The data will be available for open science, be able to attract new collaborators, and align the clinical and patient reported outcomes data and be used to determine the best outcome measures.

She said rare disease patients are different than they were 20 years ago. They recognize their data has value and they have a choice about where to put it and what to do with it. That's forcing data holders to change the way they have long operated.

"I'm not going to enroll in a study where they own all my data and I can't even access it If I could instead enroll in this program over here with an open science platform that is broadly going to accelerate disease understanding and therapeutic research by all kinds of different researchers and companies," said Trzupek. "Even companies that historically have owned some of these registries recognize now that they need to be good partners to patients and find models that make sense to allow patients to be the stewards of their own data to be able to move forward." ■

Diving Deep, Racing Fast, and Doing It Cheap

"There are savings to the healthcare system, but there's also the emotional burden, and there are times where you can actually do a better job treating the patient earlier. There are times where 24 hours can make a difference."

— Euan Ashley, Professor of Genomics and Precision Health at Stanford University

Nearly 20 years after scientists completed the draft map on the human genome, the Telomere-to-Telomere consortium finished the job. While it took the Human Genome Project about 13 years to publish what was hailed as the first complete genome, it consisted of about 92 percent of the genome: the letter sequence of As, Cs, Gs, and Ts that make up the 3 billion base pairs. The T2T consortium mapped the remaining 8 percent, a task that Eric Green, director of the National Human Genome Research Institute, hailed as a "remarkable achievement."

This consortium, which includes leading researchers at NHGRI; the University of California, Santa Cruz; and the University of Washington, Seattle, at the end of March 2022 published the complete genome extending across each chromosome without any gaps. The scientists involved in the work published six papers in the journal *Science* describing the work.

Green, in a press briefing announcing the accomplishment, explained the reason the last 8 percent of the genome took so long to map was that it consisted of "really messy stuff," long, repetitive stretches of letters that are difficult to read and difficult to assemble in the right place in the overall sequence. The regions had remained unmapped because of technical limitations of sequencing technologies.

Sequencing efforts made use of so-called "short-read" technologies that looked at a small section of genomes—hundreds of letters at a time—and then relied on computers to stitch them together in the right order. Newer sequencers can look at large sections of genomes—thousands upon thousands of letters at a time.

"Over the past two decades, all new technologies for sequencing DNA have emerged, among them methods that allow researchers to read much longer stretches of DNA at a time—from only about 500 bases back then to over 100,000 bases now—which allowed the T2T researchers to sequence

"Over the past two decades, all new technologies for sequencing DNA have emerged, among them methods that allow researchers to read much longer stretches of DNA at a time."

— Eric Green

and assemble the full length of the most difficult repeats," he said. "And so, missing piece by missing piece, the T2T team read and assembled these really rugged, repetitive bits around the centromeres, the telomeres, and the various other random places around the genome."[2]

"Short-read" technologies were originally used to sequence the human genome. Computers would take reads of several hundred bases of DNA sequence and stitch them together, but such methods leave gaps in genome sequences. The consortium used newer long-read technologies from PacBio and Oxford Nanopore to fill these gaps. Most of the newly added sequences—some 200 million letters—were in the centromeres, the centers of the X-shaped chromosomes, and the telomeres, the repetitive ends of each chromosome.

The T2T researchers have already used the sequence as a reference to identify more than 2 million variants within what they called "medically relevant genes." This holds the promise of helping to unlock the genetic underpinnings of diseases that remain hidden from researchers and could help provide answers to people suspected of having a rare genetic disease for whom whole genome sequencing has failed to provide answers.

The T2T Consortium achieved a significant milestone in 2022, but while it demonstrated the ability to do genome sequencing at a deep and thorough way, others were working to push the limits of sequencing in terms of speed and cost. Together, these advances are improving the clinical utility of whole genome sequencing and pushing it from an esoteric to routine clinical tool.

Need for Speed

Euan Ashley and his colleagues at Stanford Medicine in 2022 set a Guinness World Record for the fastest DNA sequencing technique by sequencing a human genome in just 5 hours and 2 minutes. The time to sequence and diagnose the patient totaled seven hours and 18 minutes, breaking the record previously held by Rady Children's Institute.

Ashley, professor of medicine, genetics, and biomedical data science at Stanford, used a new, ultra-rapid genome sequencing approach he and colleagues developed to diagnose rare genetic diseases in an average of eight hours. The scientists used this approach to sequence 12 genomes over a six-month period and were able to diagnose five of those patients. On average, it took eight hours to deliver a diagnosis.

Postdoctoral scholar John Gorzynski, Ashley, and others described their approach in a letter in the *New England Journal of Medicine*. "Although most critical care decisions must be made in hours, traditional testing requires weeks and rapid testing requires days," they wrote.[3]

Ashley and his team worked with colleagues at Oxford Nanopore Technologies, who built what was described as a "mega-machine" consisting of 48 sequencing units with each of those individual flow cells working on the DNA of a single patient at once. Other collaborators included researchers at NVIDIA, Google, Baylor College of Medicine, and the University of California at Santa Cruz.

The approach was so effective at generating data rapidly that it overwhelmed the lab's computer system. To address that problem, the researchers crafted a way to upload terabytes of raw data to the cloud in real time and spread that data across multiple cloud computing machines. Doing so achieved nearly real-time assembly of a genome, something that reduced the time that would be required to assemble the genome after reading by 93 percent. They were able to cut additional time through other changes, such as the way they prepared samples. The team is still refining the process and Ashley believes they can still cut their time in half.

"Maybe I shouldn't have been as bold as to say 'half' because that's quite a high bar," Ashley said laughing in an interview in October 2022.

Speed demons Euan Ashley and John Gorzynski

Credit: Stanford Medicine/Steve Fisch

"We're actually about to launch the second phase of the study and we have already worked on multiple elements of the pipeline and made them faster."

For instance, the researchers sought to strike a balance between speed and accuracy. On the first set of genomes, they decided not to use a rapid prep kit offered by Oxford Nanopore because they felt they would sacrifice some accuracy. The kit has since been improved and is expected to be used on the second phase of the work.

Ashley and his team plan to sequence people in critical care, as well as people with acute cancer. As part of this second phase, they expect to sequence trios to get the genomes of patients and their parents. They expect to sequence 50 to 100 people.

All of this, though, is not just about bragging rights but has practical consequences for patients. In the letter to *the New England Journal of Medic*ine the researchers described a 3-month-old infant who suffered from seizures. It took the team eight hours and 25 minutes to diagnose the child with Poirier–Bienvenu neurodevelopmental syndrome, which is characterized by early-onset seizures caused by a mutation to the CSNK2B gene. The diagnosis allowed physicians to scrap other testing that was planned and instead provide disease-specific counseling and management of epilepsy. Of note is the fact that the doctors had ordered an epilepsy gene panel at the time of sequencing, but that the CSNK2B gene was not a part of that panel. Not only did it fail to provide a diagnosis, but those results came in two weeks later and concluded that the infant had multiple non-diagnostic variants of uncertain significance.

In the critical care setting, there's a clear economic case for rapid sequencing. Ashley notes six hours compared to 18 hours might not sound like a big difference, but one day in the critical care unit is about $15,000 to the healthcare system. That provides a compelling return for a $1,000 investment in testing. But there are other reasons why getting a rapid answer matters.

"There are savings to the healthcare system, but there's also the emotional burden, and there are times where you can actually do a better job treating the patient by treating them earlier," he said. "There are times where 24 hours can make a difference."

Price Busting

While Stanford Medicine may be pushing to shatter the speed barrier for whole genome sequencing, others are working to accomplish similarly audacious goals with regards to reducing the cost of sequencing. Ultima Genomics, a company with the goal of using its low-cost sequencing platform to deliver a whole genome sequence for $100, emerged from stealth in 2022 with $600 million in venture backing. That represents about one-fifth of current costs.

"DNA is nature's storage media and the instruction set for every living organism, yet with current technologies, we can't access that information at the scale needed to truly understand complex biology," said Gilad Almogy, Ultima Genomics' founder and CEO, when the company unveiled itself in May 2022. "Our architecture is intended for radical scaling, and the $100 genome is merely the first example of what it can deliver. We are committed to continuously drive down the cost of genomic information until it is routinely used in every part of the healthcare system."

In a paper released on the biologic science preprint server *BioRvix*, scientists at Ultima Genomics and the Broad Institute of MIT and Harvard described the technology and its performance.

"We are committed to continuously drive down the cost of genomic information until it is routinely used in every part of the healthcare system."

— Gilad Almogy

They argued that continuous advances in sequencing technology dramatically reduced costs from the $3 billion for the Human Genome Project to less than $1,000. Nevertheless, while advances have enabled growing clinical applications, its use remains cost constrained. They said reductions in cost stalled out at around $6 to $10/Gb price. That's created a bottleneck that's forced researchers and clinicians to make tradeoffs between breadth, depth, and frequency of genomic sequencing in designing research and clinical assays because of costs.

"Currently, routine adoption of sequencing for research and diagnosis is severely constrained by cost," the authors wrote. "Over the last five years, Ultima Genomics has developed a fundamentally new sequencing architecture designed to scale beyond conventional approaches, including completely different approaches to flow cell engineering, sequencing chemistry, and machine learning."[4]

"With the clinical utility of diagnostic rWGS proven, we are using that experience to screen, diagnose, and help treat genetic conditions at or before onset of symptoms."

— Stephen Kingsmore

The push to lower the cost of sequencing, they said, will drive the development of new genomic applications and the adoption of genomic diagnostics into the standard of care. To do that, Ultima has developed a massively parallel sequencing-by-synthesis approach that combines desirable traits of current short-read methodologies within a system that provides significant scalability and dramatically lower cost.

"To enable cost-effective high-scale DNA sequencing that is both superior to current methods and amenable to continuous improvement, we have designed a sequencing architecture that efficiently utilizes economical consumables and contains multiple degrees of freedom having significant headroom for additional scalability," the authors wrote. "Our system design features three main innovative components: a) open fluidics and optics system, b) mostly natural sequencing chemistry, and c) neural network-enabled base-calling. Combined, these innovations enable scalable, high-throughput DNA sequencing and significantly reduce the consumable cost of sequencing down to $1/Gb in the first implementation, with potential for even lower costs in the not distant future."[5]

Understanding the Elusive Diagnosis

Though its long been known that many patients with rare diseases face a protracted diagnostic odyssey, the emergence and growing use of technologies like whole genome sequencing has been shortening the time it takes to get a definitive diagnosis. Nevertheless, patient experiences vary widely, and studies place the diagnostic odyssey at between four and nine years. That's likely longer for people living in low- and middle-income countries.[6] The divergence in the numbers speak to the variability of the patient experience and is in part dependent on the participants in any given survey. To understand why some patients face a protracted diagnostic odyssey, researchers from the Department of Biomedical Ethics and Public Policy at the Graduate School of Medicine at Osaka University undertook a qualitative study and focused on a group of nine patients with the rare and potentially life-threatening disease hereditary angioedema (HAE). HAE is characterized by episodes of swelling in various parts of the body. People with the condition are known to face long diagnostic delays. A 2020 survey of adult HAE patients in Japan found the average time to diagnosis was 15.6 years. It is also an example of the importance of getting a diagnosis as undiagnosed patients with HAE are three times more likely to die from the condition than those who are diagnosed.

The researchers said while there are a growing number of initiatives around the world to address undiagnosed rare disease patients and questions being raised as to whether governments are doing enough to address the problem, they argued that the experience of rare disease patients are complex and diverse and not fully understood by healthcare providers, policy makers, and other stakeholders. To get a better understanding of why patients go undiagnosed, they sought to take a deeper dive in the experience of various patients and to look for commonalities.

It took the participants in the study an average of 23 years to get an HAE diagnosis, even though most had been to a hospital within a year of

the initial appearance of symptoms. The researchers sought to understand what actions patients took to get relief from their symptoms prior to having a diagnosis, how a diagnosis was reached, and why it took so long to get an accurate answer. They found two major factors that contributed to a prolonged wait for a diagnosis. The first was that the physician and patient did not suspect a rare disease (common symptoms were abdominal pain, nausea, swelling, and vomiting). The other factor was that in cases where physicians and patients suspected a rare disease, they failed to access accurate information. Some patients stopped going to a hospital for care either because they developed mistrust in doctors or were told it was from stress or other psychological factors.

The authors said the difficulty in suspecting a rare disease found in HAE may be the case in other rare diseases as well. They say two changes would help shorten the diagnostic odyssey. The first is to improve awareness of rare diseases among medical professionals. They should be trained to recognize when a rare disease may be possible. This is true for patients as well. Beyond that, they said there is a need to improve medical systems for diagnosis by strengthening coordination of diagnosis between local clinics and higher-order hospitals and the creation of centers specialized in the diagnosis of rare diseases. In addition, they said digital tools to help identify rare disease patients through questionnaires and the use of AI tools for diagnosis could help arrive at a correct answer.

Sequencing Just a First Step

The best way to shorten the diagnostic odyssey is to eliminate it completely with newborn screening. While these tests still check for limited numbers of diseases, the use of whole genome sequencing to diagnose infants suspected of having a genetic disease has been advancing in part by innovative work being done at Rady Children's Hospital. Rady Children's Institute for Genomic Medicine is building on those efforts with a new tool designed to screen newborns before symptoms manifest themselves and provide treatment options to physicians.

In 2022 it unveiled BeginNGS, a program designed to advance and evaluate the scalability of a diagnostic and precision medicine guidance tool to screen newborns by using rapid whole genome sequencing for approximately 400 genetic diseases that have known treatment options. Once a diagnosis is made, BeginNGS uses Genome-to-Treatment, a tool that provides immediate treatment guidelines for physicians to help them understand genetic conditions and their available treatment options, which may include therapeutics, dietary changes, surgery, medical devices, or other interventions.

"With the clinical utility of diagnostic rWGS (rapid whole genome sequencing) proven, we are using that experience to screen, diagnose, and help treat genetic conditions at or before onset of symptoms," said Stephen Kingsmore, president and CEO of RCIGM. "Through a public-private consortium of leading organizations and advocacy groups in pediatrics, genetics, biopharma, biotech, and information technology, we aim to scale newborn sequencing to every life-threatening childhood genetic disease that has an effective treatment."

Stephen Kingsmore

With hundreds of new gene therapies and orphan drugs in development, Kingsmore said Rady Children's Institute for Genomic Medicine believes it is now the time to end the diagnostic and therapeutic odyssey for all children with treatable genetic diseases.

The institute is currently in the beginning stages of a pilot evaluation, which includes optimizing automated genomic sequencing and analysis, with the goal of curating a high-quality set of variants to enable testing for approximately 400 genetic disorders. In subsequent stages, study enrollment will begin, followed by system optimization and testing expansion to approximately 500 disorders and several thousand cases. The goal is for BeginNGS to become the genetic disease screening standard, with testing expanding to about 1,000 disorders and sequencing of 3.7 million newborns annually.

Genetic Testing Significantly Underutilized in the Clinic

There's significant underutilization of genetic testing and substantial delays for pediatric patients suspected of having a genetic disease to get testing, according to a study in the journal *Genomic Medicine*."[7]

The study from November 2021 and funded by the sequencing giant Illumina examined claims data from more than 13 million patients in the United States. The researchers identified patients who showed signs of a genetic condition, such as intellectual disability, developmental delay, multiple congenital anomalies, or epilepsy—conditions that multiple society guidelines indicate these patients should get genetic testing.

The researchers found that only about 5 percent of the patients who showed signs and symptoms of a genetic disease received any kind of genetic testing. On average, it took about 473 days for them to get a test from first presentation in the clinic.

When asked why genetic testing is not performed more often in cases where it should be used in the clinic, Ryan Taft, vice president of scientific research at Illumina and one of the authors on the study, said the study didn't address that question. He suggested, though, it could be a combination of reasons.

"I think this does come down to reimbursement for a lot of these tests. Is it possible for a clinician to order this test and actually have it reimbursed? As we know, policies across the U.S. are highly variable, they're often difficult to manage. Our system isn't great at making sure these patients can get the right test at the right time from a reimbursement standpoint," he said. "The second is education and that's at multiple levels."

"I personally have never worked on a case where providing a diagnosis didn't have an impact on the patient or that family."

—Ryan Taft

In terms of education, he said that includes making sure administrators understand the value of molecular testing, as well as clinicians who need to understand the impact these tests will have on their patients, and then patients and their families. Taft believes there's both a patient and an economic case to be made for genetic testing.

"I personally have never worked on a case where providing a diagnosis didn't have an impact on the patient or that family," he said. "We're stopping the diagnostic odyssey, stopping unnecessary testing. We're often providing a psychological salve. We're providing that family an answer. We're stopping that psychological anguish. We often put these patients on the right supportive care pathway."

From an economic perspective, he said there is increasing evidence that whole genome sequencing is going to provide cost saving. He pointed to a study in *Genetics and Medicine* that colleagues of his at Illumina conducted that looked at both pediatric patients and neonates and compared standard of care testing (which involves multiple molecular genetic tests) to genome sequencing. It found that at worst, genome sequencing is cost neutral, and at best, it's likely to be cost saving.

"We're seeing more and more evidence that this is the right thing to do for the patients," he said. "Not just because it puts them on the right care pathway, but because it's going to save the system money."

BeginNGS aims to supplement existing newborn screening protocols at birthing hospitals throughout the United States. Blood-spot samples will be collected at the time of birth and sent to a lab where rWGS, genomic analysis, and interpretation will be performed for approximately 400 early onset and actionable genetic conditions. When a positive screening result is detected, a confirmatory diagnostic interpretation will be completed before a result is returned to the ordering physician. Additionally, physicians will be provided with guidance on known medical management options including all available treatments through GTRx, a virtual automated system for immediate clinical management of childhood genetic diseases.

Founding members Alexion, AstraZeneca Rare Disease, Travere Therapeutics, and Inozyme Pharma will play a critical role in helping advance the program towards a change in approach to newborn screening for treatable rare genetic diseases. The BeginNGS consortium will include representation from patient advocacy groups and the biomedical ecosystem, who will collectively provide strategic and technical expertise.

Of nearly 4 million babies born annually in the United States, 98 percent are tested in the first days of life with newborn screening for serious childhood diseases that have effective treatments. States currently screen for between 31 to 76 of the hundreds of severe, childhood genetic diseases that have available treatments. Adding a new condition to the screen requires going through a long, costly, and intensive process. At the same time, whole genome sequencing has increased in speed, diagnostic performance, and scalability. Rady's said BeginNGS will not replace the current biochemical newborn screening but complement the processes and infrastructure that are already in place.

"Newborn screening is often misunderstood and will only be done in indications that have an approved therapy. Only once there's a therapy approved can you start the addition to the newborn screening protocol and it's actually a state-by-state thing. So, if we wanted to get our disease on newborn screening, we would be waiting," said Axel Bolte, CEO of Inozyme Pharma, one of the founding members of the BeginNGS program. "The idea is that the BeginNGS platform will leapfrog that because of the power of whole genome sequencing and just immediately make all the genomic information available and significantly improve early detection of these rare diseases across all rare diseases."

Finding Answers

While the falling price of whole genome sequencing has spread its use as a clinical diagnostic tool that may allow people with rare disorders to finally get a diagnosis, it's still true the case that more than half of the time whole genome sequencing will not result in a definitive diagnosis. Instead of having a name to put to their disorder, they may simply be told that they have a "variant of unknown significance."

As researchers gain access to more whole genome sequencing data, it is increasingly recognized that mutations in regions of the genome that do not directly encode protein can play an important role in genetic diseases. The problem is that while whole genome sequencing is uncovering a growing number of potentially pathogenic variants, there is a lack of systematic criteria to determine if they are in fact causing a genetic disease.

An international group of scientists in July 2022 published recommendations for updating existing standards for determining the disease-causing potential of genomic variants to enable clinicians and researchers to take better advantage of the full range of variation in whole-genome sequence data. The work, led by scientists at Genomics England, included experts from academic and healthcare institutions across the United Kingdom, United States, and Australia.

The recommendation, published in a paper in July 2022 in the online edition of the open-access journal *Genome Medicine*, noted that most genetic testing has been focused on coding sequence variants that disrupt regions of genes that directly encode proteins.[8] The standards and guidelines developed over the past decade

"Only once there's a therapy approved can you start the addition to the newborn screening protocol, and it's actually a state-by-state thing."

—Axel Bolte

Children's Mercy Genomic Answers for Kids Program Diagnoses 1,000th Rare Disease Patient

Just three years after the Children's Mercy Research Institute launched the Genomic Answers for Kids (GA4K) program, the program in September 2022 reported that it had hit the milestone of providing 1,000 rare disease diagnoses to families.

One reason for the success has been the use of so-called 5-base HiFi sequencing, which captures the full genome and methylome to reveal part of the human genome that has never been clinically tested and interpret changes beyond the genetic code, according to Tomi Pastinen, director of the Genomic Medicine Center at Children's Mercy Kansas City. Of the 1,000 diagnoses the program has made, 300 relied on 5-base sequencing.

"On average, only 30 to 40 percent of rare disease cases are diagnosed," he said. "What we are doing is giving those remaining 60 percent of families hope that we'll find answers by discovering relevant gene variations in long-read sequencing only detectable by using this technology."

GA4K, backed with $18.5 million in philanthropic funding, is a first-of-its-kind pediatric data repository. The goal is to collect genomic data and health information for 30,000 children and their families over seven years to create a database of 100,000 genomes.

HiFi sequencing offers several advantages over short-read sequencing. Because it is capturing sequences that are 100-fold the size of short-read sequencing, it can capture complex and structural variations in the genome rather than just single nucleotide mutations. This can include insertions of new pieces of DNA that are multiple base pairs in length, or deletions including removal of DNA pieces of hundreds and thousands of bases in length. That, said Pastinen, is not possible with short-read sequencing.

"What we are doing is giving those remaining 60 percent of families hope that we'll find answers by discovering relevant gene variations in long-read sequencing only detectable by using this technology."

— Tomi Pastinen

In addition, he said HiFi sequencing reads are very accurate and the 5-base readout includes not only As, Cs, Gs, and Ts, but also methylation of DNA, a novel feature that became available in 2022.

Children's Mercy is collaborating with other institutions to help them diagnose rare disease patients who have gone undiagnosed. It has been able to solve cases for them using HiFi genome sequencing. It's also building what is already the world's largest disease-oriented long-read sequencing database. It provides that to other groups that are pursuing their own HiFi genome sequencing rare disease programs as a background database where they can compare their own sequences to its large data repository.

Ultimately, Pastinen believes that a critical issue for expanding the diagnosis of rare disease patients will be to get payers to provide reimbursement for these new technologies.

"We do want to provide sufficient scientific evidence and follow up evidence so that would help the insurers to accelerate their plans for reimbursement for this modern molecular test," he said. "Short-read sequencing has benefited from over 10 years of community efforts in building these reference databases. We're only in the start with this long-read genome sequencing and its full benefit comes into life when multiple groups start to use it, and, like us, share the data with the community to build that large resource to compare every new patient sequence and to extract all the benefits from the long-reads and the 5-base sequence."

for interpreting the results of these tests—including single-gene assays, gene panels, and whole-exome sequencing—have focused on these types of variants. While that's resulted in consistent and reliable diagnosis for diseases resulting from mutations in the coding regions of the genome, it represents less than 2 percent of the entire genome. The authors recommend adaptations and expansions that are designed to supplement the existing guidance and make use of the same approach of consultation and consensus-building that was used to create them.

It's not just whole genome sequencing that is uncovering new variants of unknown significance, but also new long-read sequencing that is also allowing researchers to uncover variants that may have gone undetected with the use of short-read sequencing. PacBio, which has developed long-read sequencing technology, in April 2022 entered into a collaboration with Genomics England to use PacBio's technology to identify genetic variants in cases where patients appeared to have an undiagnosed rare disease. The collaboration is part of a broader effort on the part of PacBio to demonstrate the benefits of so-called HiFi sequencing to identify rare diseases.

Under the collaboration, Genomics England will re-sequence a selection of samples collected during its 100,000 Genomes Project, which were previously analyzed with short-read sequencing technology. The study is intended to demonstrate benefits of long-read sequencing in identifying genetic mutations associated with rare diseases. The collaboration follows similar recent announcements of PacBio's rare disease-focused research collaborations with Radboud University Medical Center, Care4Rare Canada Consortium, ARUP Laboratories, UCLA Health, Rady Children's Institute for Genomic Medicine, and Children's Mercy Kansas City.

"The 100,000 Genomes Project was able to find actionable mutations in around 25 percent of patients with rare disease," said Parker Moss, chief Ecosystem and Partnership officer at Genomics England. "We are hopeful that additional insight gained during the study may, ultimately, lead to new therapeutic or clinical trial options for patients with rare disease."

Making Advances for All

While advances to genomic sequencing have been shown to be a powerful tool for diagnosing people with a genetic disease, there is growing concern that people in low- and middle-income countries may not benefit equally from its advent as those in wealthier countries. In a position statement published in the *Orphanet Journal of Rare Disease* in May 2022, a group of patient advocates from around the world note while financial obstacles to the global adoption of sequencing technologies as a clinical diagnostic tool are an obvious barrier, there are other socio-cultural obstacles that need to be addressed if the technology is to be made available equitably across the globe.[9]

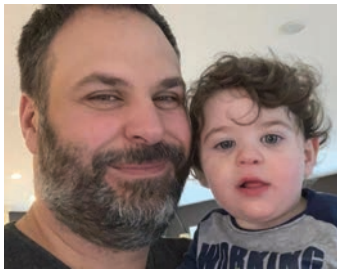
The authors argue that in addition to financial ability and health service infrastructure, issues like geography, language, communication, and culture all play a role in the adoption of genomic medicine. To address current disparities, they say it will be necessary to address these other issues in addition to the more recognized barriers. For instance, they note religious beliefs, such as ones that view suffering as the result of bad acts in a previous life, can change the view on a rare disease diagnosis and the effort to access medical technology. Shame and social stigmas linked to people living with a rare disease can also serve to prevent someone from seeking a diagnosis. In addition, in many countries there may be a lack of understanding that a mutation in a single gene can cause a devastating illness and the authors say public education and advocacy are essential.

People living with rare diseases in low- and middle-income countries have an opportunity to benefit from the advances to improved understanding of the genetic cause of disease and the falling cost of sequencing, but to do so will require approaches that are tailored to local communities with consideration of cultural factors, the authors said. "It is clear that while much of the focus on barriers to genomic medicine adoption is on health systems and financial constraints," they write, "an increased focus on sociocultural and community factors is critical for delivering insights for a broader and more global implementation of genomic medicine." ■

"The 100,000 Genomes Project was able to find actionable mutations in around 25 percent of patients with rare disease."

— Parker Moss

The Promise and Peril of Genetic Medicine



"We needed a team of hundreds of people. People think that the scientists and everybody else are important, but everybody along this food chain, as I call it, is important."

— Terry Pirovolakis, Founder CureSPG50

In March 2022, a team at The Hospital for Sick Children in Toronto administered an experimental gene therapy to Michael Pirovolakis, a four-year-old child with the ultra-rare genetic condition spastic paraplegia type 50, in a single-patient clinical trial.

Doctors at SickKids diagnosed Michael in 2019 at the age of 1. At the time, he was the only child in Canada believed to have SPG50. There are now about 80 known people worldwide who have the condition. SPG50 is a progressive neurodevelopmental disorder that causes developmental delays, speech impairment, seizures, and a progressive paralysis of the limbs. The condition can be fatal.

Following Michael's diagnosis, his parents Georgia and Terry Pirovolakis launched CureSPG50. Through a GoFundMe page and a list of events including golf tournaments, bowling tournaments, bike rides, dance-a-thons, bingo nights, lemonade stands, garage sales, gyro night, and more, the organization raised $2.7 million (CAD 3.5 million) to fund the development of a gene therapy that could help Michael and other people with SPG50. The organization enlisted researchers at University of Texas Southwestern Medical Center, the National Institutes of Health, and Boston Children's Hospital to develop and test a gene therapy.

The gene therapy, dubbed Melpida, derives its name from the combination Michael and "elpida," the Greek word for "hope." The one-time gene replacement therapy replaces the defective gene with a functional version. The clinical study will compare Melpida's effectiveness in children to a natural history study of SPG50 patients.

Michael was doing well following the treatment and his father said there are some indications his symptoms may be improving. He will be monitored over time to see whether the therapy effectively slows the progression of his disease and potentially reverses some of its impacts. But the work hasn't stopped for the Pirovolakis family and CureSPG50. It is working to establish clinical trials for other children with SPG50 and to continue testing the therapy. It estimates it will need to raise $250,000 for each child that will get treated with the gene therapy.

The development of the SPG50 gene therapy was accelerated by leveraging the work UT Southwestern's Steven Gray had done to develop a gene therapy for another rare neurodevelopmental condition and by a decision on the part of Pirovolakis to take the financial risks of conducting experiments in parallel rather than waiting for the results of one experiment before beginning the next experiment. It also required a deep level of commitment from many people along the way.


Steven Gray

"We needed a team of hundreds of people," Pirovolakis said. "People think that the scientists and everybody else are important, but everybody along this food chain, as I call it, is important."

For example, Pirovolakis said the organization shipped a batch of the gene therapy from Spain to Quebec, and it was delayed on route because of a snowstorm. The gene therapy needed to be kept cold with dry ice, which meant that it had to be replenished every day for four days or the batch would be lost and it would take months to remake. A representative from Charles River Labs, who manages "shipping" was on the phone for hours talking to the shipping company to make sure that someone replenished the dry ice and he called back every day for confirmation.

"This is the type of dedication that is along the whole pipeline that you have to get to, because if you lose anything along the way, you're set back potentially a year," said Pirovolakis. "We were just fortunate we had this amazing group of people that just fully understood that we're trying to save kids."

Gray said one other critical factor in the speed of their progress was a result of the partnership he had with Pirovolakis and CureSPG50, which he said could be held up as an example of how to do this by allowing the scientists to do their work without distraction.

"Terry let me focus on the research and moving everything forward and he handled all the fundraising," he said. "We never spent any time trying to write external grants. He was very


Michael Pirovolakis with his parents Terry and Georgia at SickKids in Toronto.


Michael Pirovolakis

active in engaging some of the contract research organizations and the manufacturers, so that my lab could just focus on the technical aspects of moving this forward."

Challenges Persist

The emerging area of genetic medicine has faced a number of challenges. These include the durability of these medicines, the ability to deliver them to desired cells and tissue throughout the body, as well as their safety. In principle, genetic medicines provide an elegant way to correct, compensate, or disrupt the work of faulty genes. In practice, though, developing safe and effective genetic medicines continues to face hurdles. The industry has come far since the 1999 death of Jesse Gelsinger, an 18-year-old participant in a trial for a gene therapy to treat the rare, metabolic condition OTC deficiency. Gelsinger died from an immune response to the experimental gene therapy, and his death continues to cast a long shadow as regulators seek to balance concerns over safety, the need for adequate proof of efficacy from small trial populations, and concerns over whether these therapies will provide lasting benefits.

In August 2022, Novartis reported that two children treated with its approved gene therapy Zolgensma for spinal muscular atrophy, a rare and fatal neuromuscular condition, had died from acute liver failure. Acute liver failure is a known side effect of Zolgensma and noted in a black box warning with the therapy. *STAT* first reported the deaths, which occurred in Russia and Kazakhstan. The deaths occurred at approximately five to six weeks post-Zolgensma infusion, and approximately 1 to 10 days following the initiation of corticosteroid taper, Novartis said in an emailed statement. "While this is important safety information, it is not a new safety signal and we firmly believe in the overall favorable risk/benefit profile of Zolgensma, which to date has been used to treat more than

From Mila to Millions

When Julia Vitarello learned that her daughter Mila had the CLN7 form of the deadly, neurodegenerative condition Batten disease, it set her off on a search for a treatment that resulted in the development of the first, customized antisense oligonucleotide to treat a patient.

Vitarello engaged Boston Children's Hospital researcher Timothy Yu, who devised the antisense oligonucleotide therapy dubbed "Milasen," and led the effort to develop, test, and advance the therapy. In 2018, Mila received the tailored medicine. Though she died in 2021, Vitarello said the therapy suppressed Mila's seizures and improved her quality of life.

The work on Milasen ignited the imagination of the rare disease community, which recognized the potential to quickly develop customized therapies for ultra-rare disease populations that would be too small to attract the interest of a drug company. To enable the development of such therapies, and to go, as Vitarello says, "from Mila to Millions," she and Yu founded the N=1 Collaborative.

The N=1 Collaborative brings together an international network of experts working to address the challenges of creating individualized treatments for rare disease patients safely and quickly. It received founding support from the Oligonucleotide Therapeutics Society N-of-1+ Taskforce and the Chan Zuckerberg Initiative.

"When we launched it, the purpose of it was to see how do we make what we did for Mila something that can be applied across many rare diseases?" said Vitarello. "How do we make individualized medicines safely, which is important, but rapidly accessible to patients worldwide?"

The N=1 Collaborative said it is working to establish a standardized framework for individualized medicine beginning with ASOs but extending to other customizable platform technologies such as siRNAs, RNA therapeutics, and CRISPR as well. It has workgroups focused on critical steps in the development of an individualized drug, with an emphasis on data sharing and establishing best practices. These include such things as patient

2,300 patients worldwide across clinical trials, managed access programs, and in the commercial setting," Novartis said in its statement.

The Zolgensma incident was not unique. In December 2021, Pfizer halted enrollment in an early-stage trial of its experimental gene therapy for Duchenne muscular dystrophy after the death of a young male patient in the non-ambulatory arm of the study, and Astellas Gene Therapies (formerly Audentes), reported in September 2021 that a fourth child in a study of its experimental gene therapy for the rare neuromuscular disease X-linked myotubular myopathy, died after a serious adverse event. Astellas Pharma would later in 2022 take a $560 million impairment charge after reassessing the timeline to an approval, the eligible treatment population, and the anticipated product label. The company dropped several gene therapy programs and terminated the development of three gene therapy programs for Duchenne muscular dystrophy based on preclinical data.

Along with these deaths, there have been a spate of clinical holds placed on gene therapy trials in recent years reflecting regulators' concern and caution about the safety of these new therapies and the difficulties gene therapy developers have faced. In June 2022, the FDA placed a clinical hold on Astellas Gene Therapies' experimental gene therapy AT845 for the lysosomal storage disorder Pompe disease after a serious adverse event of peripheral sensory neuropathy in one of the trial participants. In February 2022, the agency placed a clinical hold on Homology Medicines' phase 1/2 study of its experimental gene therapy HMI-102 for adults with the rare metabolic condition phenylketonuria after elevated liver function tests were observed during a clinical study. Larimar Pharmaceuticals, Mustang Bio, Voyager Therapeutics, Bluebird Bio, and Rocket Pharmaceuticals all faced clinical holds to gene therapy programs in 2021.

Even when companies avoided regulatory snafus, they had to face the reality of what clinical

"We need to drive down the requirements to be correct and proportionate—still safe, absolutely, but correctly proportionate, which is going to require a new mindset."

—Julia Vitarello

selection criteria, drug design, validation, and safety assessment; clinical trial design and outcome measures; trial implementation within institutions; and ethics, equity, and accessibility.

While N=1 is working to tackle the scientific issues N-of-1 therapies face, Vitarello said there's also a need to think about how to create a viable business model that includes reimbursement.

"Milasen fell in this no man's land between research and compassionate use, and that didn't exist before. It's currently not reimbursable and that needs to change," she said. "I want to make sure that there is a sustainable model and having academics spend two years, $2 million, and a thousand-page IND, with 30 people in their institution working on something for one individual child is not scalable and it's not sustainable."

Vitarello believes an important starting point down the road to sustainability will be for the U.S. Food and Drug Administration to establish an appropriate regulatory path for N-of-1 therapies. She said one significant way to reduce the cost of development is to establish toxicity and safety requirements that are proportionate to creating a therapy for a handful of patients.

"What I say is we climbed Mount Everest to make Milasen happen. Some others can do that as well, but how many people can climb Everest? Not that many and that mountain has to be significantly lower," said Vitarello. "It has to be small enough that anyone who could benefit from an individualized ASO should have access to it right now. We need to drive down the requirements to be correct and proportionate—still safe, absolutely, but correctly proportionate, which is going to require a new mindset."

trials data told them. In January, Avrobio said it would stop enrollment in a clinical trial of its Fabry disease gene therapy, its most advanced program, to shift priorities to other clinical-stage programs and extend its cash runway into the first quarter of 2024. It made the decision after clinical data showed variable engraftment patterns from patients dosed in its phase 2 FAB-GT study. It also attributed the decision to the challenging market and regulatory environment for Fabry disease. The company said that it believes, due to the large degree of heterogeneity in Fabry disease, that in some cases there may be intrinsic resistance to engraftment related to the unique underlying pathophysiology of untreated Fabry disease.

"There was initially a lot of excitement around gene therapy as once and done, but it looks like that's not the case. AAV viral vectors don't self-replicate."

— Carsten Brunn

Next Generation Vectors Advance

As a first generation of genetic medicines is reaching the market, emerging technologies are advancing to address key challenges of durability, targeting, and immunogenicity to make these life-altering medicines safer and more effective. Despite the difficult fundraising environment in 2022, several companies developing genetic medicine technologies and platforms completed significant financings and entered into partnership agreements during the year.

Selecta Biosciences is using its ImmTOR platform technology to address problems of immunogenicity with the potential of transforming therapies using viral vectors into redosable treatments. Even though gene therapies are billed as one-and-done treatments, their benefits may fade over time. Though replacement gene therapies deliver functional copies of genes within the cellular machinery, these genes are not integrated into the genome. As new cells replace old cells, the number of cells with a functional copy of a needed gene diminish. And once a patient has been exposed to a specific viral vector, the patient's immune system will train itself on that gene vector and attack it if exposed again.

Selecta is developing a pipeline that is much broader than gene therapies, as it can be used to address immunogenicity in biologic therapies including enzyme replacement therapies, as well as the development of therapies to treat autoimmune diseases. The company's ImmTOR platform works by using nanoparticles that deliver rapamycin, an immunosuppressive drug long used to prevent organ rejection, to train the immune system to ignore specific antigens, such as a viral vector.

"There was initially a lot of excitement around gene therapy as once-and-done, but it looks like that's not the case. AAV viral vectors don't self-replicate. That means over time, the cells get diluted down and you see a loss of expression, and there's plenty of examples now out there where we clearly see that over time expression goes down, efficacy goes down, and because it's a viral vector, it's highly immunogenic. The body develops neutralizing antibodies, and you can't give a second dose," said Carsten Brunn, CEO of Selecta Biosciences. "We give ImmTOR with the first dose of AAV gene therapy to prevent the formation of neutralizing antibodies. We're able to demonstrate this in a healthy volunteer study with an empty AAV capsid, so no transgene. We're able to prevent the formation of neutralizing antibodies in a certain timeframe, which is very exciting and opens up pretty broad applicability across liver directed AAV gene therapy."

Selecta has entered into partnerships with AskBio, Sarepta, and Takeda over the development of multiple gene therapies, as well as developing its own pipeline of gene therapies and biologics. It completed a $38.7 million offering of common stock and warrants in April 2022 to strength its finances.

To address the limitations of adeno-associated viral vectors and lentiviral vectors, several companies are developing alternative vectors that don't create an immune response in humans. For instance, Gensaic is developing a new class of *in vivo* gene delivery vehicles by looking to phage-derived particles. Phages are viruses that are highly selective and kill bacteria. These so-called PDPs can be designed with high affinity targeting molecules on its coat and can carry cargos more than four times the size of AAV's limits. PDPs also have the benefit of being pro-

A Closely Watched N-of-1 Study Ends in the Death of a "Medical Pioneer"

Terry Horgan, the only participant in a trial of an experimental CRISPR therapy designed to treat his particular form of Duchenne muscular dystrophy, died October 14, 2022. He was 27.

The effort to treat Terry Horgan, the brother of Cure Rare Disease founder Rich Horgan, was one of the most closely followed efforts to develop N-of-1 therapies for people with rare diseases. The cause of death was not disclosed, but Cure Rare Disease said it is working with researchers to understand the outcome of the study of the experimental therapy known as CRD-TMH-001.

"Cure Rare Disease was founded with a commitment to transparency and collaboration as we believe both are critical to moving science forward for rare disease patients," Cure Rare Disease said in a blog post on its website. "To that end, we intend to share the findings from the CRD-TMH-001 trial with the scientific community, not only to support the continued advancement of the additional 18 therapeutics in the CRD pipeline, but also to further the understanding of AAV-based gene


Rich Horgan


Terry Horgan

therapies and applications among the larger communities for the treatment of other rare diseases."

The death of Terry Horgan is a painful reminder that despite the elegance of genetic medicines and their potential to provide one-and-done treatments for people with genetic diseases, much is still unknown. Patients and researchers may be driven by optimism for the potential of these emerging therapies, but despite promising approaches, participants in such studies are taking personal risks for the advancement of science.

Terry Horgan was diagnosed in 1999 with Duchenne muscular dystrophy, a rare and fatal muscle-wasting disease caused by a mutation in the gene that codes for production of the protein dystrophin. Though much work has been done to develop treatments for the condition, none of the approved therapies were appropriate for Terry's particular form of Duchenne and as a person in his twenties, he was considered too old to participate in most clinical trials for the condition.

As a student at Harvard Business School, Rich Horgan began reaching out to researchers to learn about his brother Terry's condition and see what could be done to accelerate efforts to find a cure. He was taken with the work of Timothy Yu, a researcher at Boston Children's Hospital who had developed a customized antisense oligonucleotide therapy for a young girl with a rare neurological condition. Horgan founded the nonprofit organization Cure Rare Disease to develop customized therapies to treat patients with rare, genetic conditions.

In August 2022, Cure Rare Disease reached a milestone when it won FDA approval to administer CRD-TMH-001, an experimental CRISPR therapy to treat a form of muscular dystrophy. CRD-TMH-001 is designed to upregulate an alternate form of the dystrophin protein using CRISPR technology with the goal of stabilizing, or potentially reversing, symptom progression of Duchenne muscular dystrophy.

"The loss of Terry is heartbreaking, and he will be remembered as a hero. He was a medical pioneer whose courage and unflinching determination has paved the way for increased focus and attention on funding and developing new therapies for patients with rare and ultra-rare conditions," Cure Rare Disease said in a blog post announcing his death. "Terry's legacy will live on and Cure Rare Disease will continue to fight for patients like him who are running out of time and options."

A Setback for N-of-1 Therapies Is a Reminder of the Need to Share Data

Valeria Schenkel, a child with a rare epilepsy who was treated with a customized antisense oligonucleotide, died from a build-up of fluid in her brain as a result of the treatment, according to a report in October 2022 in *The New York Times*.

Schenkel had KCNT1-related epilepsy, an ultra-rare, genetic, seizure disorder. The newspaper noted she suffered from dozens of seizures a day and was unable to sit up or speak. Half of the children with the condition die by the age of 3.

Timothy Yu, a neurologist and genetics researcher at Boston Children's Hospital, who has pioneered development of N-of-1 therapies for ultra-rare conditions, developed the therapy known as valerisasen. The occurrence of hydrocephalus, because of the treatment, was reported at the American Neurological Association meeting in Chicago.

A second child who was treated with the valerisasen also developed hydrocephalus and nearly died last year.

"I think it's worth saying: No question that encountering hydrocephalus has been a setback, sobering and important," Yu told *The New York Times* as he noted that traditional drug companies are not helping patients with thousands of rare, untreatable, and rapidly progressing diseases that cause death and severe disabilities. Personalized genetic treatments, he said, may be their only hope.

The precision and elegance of genetic medicines are compelling, but the death is a painful reminder to proponents of N-of-1 therapies that these treatments come with risks. Even for parents of children with fatal conditions, the decision to pursue such treatments can be difficult because of fear of doing more harm than good. But if there's a takeaway from this story, it is that the best way to minimize risk and maximize the benefits of these therapies to patients is not to be timid in pursuit of treatments but to share data so we can collectively learn as much as possible about them.

"We have to learn as much as we can from each and every one because they're just so incredibly valuable in every sense."

—Timothy Yu

Roche in 2021 reported that three patients in a clinical trial treated with an experimental antisense therapy for the rare, neurodegenerative condition Huntington's disease developed hydrocephalus. *The Times* also noted some patients treated with the approved antisense therapy nusinersen have developed hydrocephalus, but the fluid build-up is a problem for many neurological conditions. Whether there is a problem using ASOs to treat these conditions remains unclear.

Erika Check Hayden, who wrote the story, notes "The new reports underscore the need for researchers to share data on experimental drugs that are tested in only one or a few people." While the FDA must approve the clinical studies of an experimental personalized therapy, there is no requirement that researchers share their data.

The development of therapies for small patient populations is riddled with obstacles. These are only amplified when developing N-of-1 therapies. People who are devoting themselves to advancing therapies fall short of doing what they can for people with rare disease when they don't share data they have, particularly when things to go well.

"We have to learn as much as we can from each and every one," Yu told Hayden, "because they're just so incredibly valuable in every sense."

duced with a scalable manufacturing cell line. Gensaic said it can produce clinical doses at a cost that is 100 times less than AAV gene therapies. And because they are engineered from a phage that's readily found in the human microbiome—billions of phages are in our bloodstreams—it is immune-privileged allowing for redosable gene therapies.

In August 2022, Ovid Therapeutics entered into a strategic collaboration with Gensaic to develop up to three genetic medicines for CNS indications using its PDP platform. As part of the agreement, Ovid invested $5 million in convertible preferred stock in Gensaic as part of the deal. Ovid will have commercial rights to license and develop any resulting phage-derived gene therapies that emerge from this collaboration subject to agreed-upon terms. Ovid also retained rights to invest in future rounds.

"This phage-derived platform appears to be optimal for crossing the blood-brain barrier with substantial genetic cargo, and we believe it may hold the potential to treat a broad continuum of diseases of the brain," said Jeremy Levin, CEO of Ovid.

Ring Therapeutics, which in July 2022 raised $117 million in a series B venture financing, has assembled an anellovirus database with thousands of anello-based vector candidates. Anelloviruses don't cause harm to humans and are present throughout the population. Ring has developed a platform to harness the properties of anelloviruses to generate an array of vectors that can target specific tissue within the body and allow for redosing without causing an adverse immune response.

Other companies are looking beyond viral vectors to liquid nanoparticles or LNPs. These delivery vehicles have already been used in approved therapies. In 2018, Alnylam won approval for its RNAi therapy for the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. Onpattro uses a lipid nanoparticle as the vector to carry its oligonucleotide payload. These vectors can be constructed to carry mRNA, RNA, or DNA therapeutics. Acuitas Therapeutics, which is developing a wide range of LNP vectors, entered into a partnership with Arbor Biotechnologies to use Acuitas's LNP technology for CRISPR gene editing therapies for rare liver diseases. LNP are well suited for efficiently targeting hepatocytes with limited off-target effects and minimal immunogenicity.

ReCode Therapeutics completed a $120 million extension to its series B financing in June 2022 to fund the diversification of its LNP platform to deliver a wider range of genetic medicine cargoes including gene correction therapies and siRNA therapies to a wider range of target cell types in a predictable and programmable way. The company is working to advance mRNA programs for primary ciliary dyskinesia and cystic fibrosis into the clinic.

ReCode's selective organ targeting (SORT) LNP delivery platform is engineered to enable improved efficacy and potency of genetic therapies by delivering them directly to the organs and cells most impacted by disease. It said genetic medicines have been limited by first-generation LNP, which are primarily taken up by the liver, limiting their utility for broad therapeutic applications. The company's platform technology can not only handle a range of genetic cargo but also be administered through a variety of means including IV, inhaled, subcutaneous, intramuscular, and intrathecal delivery.

At the American Thoracic Society 2022 International Conference in May 2022, the company presented preclinical data from its programs in primary ciliary dyskinesia and cystic fibrosis that demonstrated that selective organ targeting LNP-formulated therapeutic candidates can be precisely delivered directly to disease-relevant cells without significant exposure to other tissue, effectively releasing the encapsulated genetic cargo and expressing the correct proteins at relevant levels.

ReCode was not the only company to attract the attention of investors with the promise of redosable gene therapies. Krystal Biotech completed a $200 million public offering at the end of 2021 to advance its pipeline of gene

"This phage-derived platform appears to be optimal for crossing the blood-brain barrier with substantial genetic cargo."

—Jeremy Levin

therapies to treat conditions of the skin. It's developed a gene therapy platform for skin targeted delivery that involves an engineered herpes simplex virus-1 vector with its skin optimized gene transfer technology. It is applied locally and can be delivered either topically or intradermally.

The U.S. Food and Drug Administration in August 2022 accepted Krystal's application for marketing approval of its lead gene therapy program B-VEC for the treatment of dystrophic epidermolysis bullosa, a severe disease that affects the skin and mucosal tissues. B-VEC is a non-invasive, redosable gene therapy that is applied topically. It provides patients with functional COL7A1 gene, which produces type VII collagen. This protein forms anchoring fibrils that bind the dermis to the epidermis. The lack of these fibrils in people with DEB causes blisters and tears from minor friction or trauma.

"The fundamental challenges with oligonucleotides have been that of delivery, and it's been that of successful delivery outside of the liver."

—Sarah Boyce

Targeting With Precision

While early genetic medicines have targeted easier to reach tissue, such as the liver, brain, and eye, a new generation of companies are developing platforms to selectively target tissue throughout the body. This is essential to realizing the potential for these new modalities and delivering them in safe and effective ways.

Code Biotherapeutics, which completed a $75 million series A financing in June 2022, is developing genetic medicines using its non-viral, synthetic, 3DNA delivery platform to develop gene therapies, RNAi, and other genetic medicines that target specific cells. The 3DNA platform leverages targeted molecules including peptides, antibodies, and small molecules that bind to cell surface proteins expressed on target cells. This allows it to target cells with specificity beyond the liver while reducing the risk of immunogenicity and enabling redosing. It's lead program is a gene therapy to treat Duchenne muscular dystrophy.

In February, the company's approach won validation with the signing of a collaboration with Takeda to use the 3DNA delivery platform to develop gene therapies. The two companies will work together to develop a targeted gene therapy for a liver-directed rare disease program and conduct additional studies for central nervous system-directed rare disease programs. The deal gives Takeda the right to exercise options for an exclusive license for four programs.

Under the terms of the agreement, Code Bio will receive a multi-million upfront payment, and near-term milestone and research funding payments. Code Bio is also eligible to receive future development and commercial milestone payments plus tiered royalties with a potential total deal value over the course of the partnership of up to $2 billion if milestones for all four programs are achieved. Takeda and Code Bio will collaborate on research activities up to candidate selection. Takeda will assume responsibility for further development and commercialization after it exercises an option.

RNA therapies are a proven approach to treating genetic diseases. The benefits of the therapies, however, have been limited by the challenge of being able to target cells and tissue throughout the body. One solution being pursued by some companies is to conjugate ASOs with targeting mechanisms.

"The fundamental challenges with oligonucleotides have been that of delivery, and it's been that of successful delivery outside of the liver. You can deliver oligonucleotides very successfully to the liver. There are many therapeutics that have come out of being able to do that, but delivery to other cells and tissue types has been a fundamental challenge," said Sarah Boyce, CEO of Avidity Biosciences. "We're an oligonucleotide delivery company and we're using the antibody as that delivery mechanism to get our oligo to cells and tissue types that haven't been achievable before like for example, muscle cells."

Avidity Biosciences has developed a platform for antibody oligonucleotide conjugates (AOCs) that combines the specificity of monoclonal antibodies and the precision of oligonucleotides. The company said integrating these proven

A Drug Repurposing Proponent Launches Nonprofit to Find Generic Drugs That Can Treat Rare Diseases

As a medical student, David Fajgenbaum became a big proponent of repurposing drugs while facing death from the rare immune condition Castleman disease after he was able to identify an already approved drug for a different indication that could be used to save his own life.

Now, with the backing of the Clinton Global Initiative, Fajgenbaum has co-founded Every Cure, a nonprofit, data-driven hub that seeks to accelerate connections between drugs and diseases they may be able to treat.

USA Today reported on the launch of Every Cure saying it was seeking to raise $55 million to identify generic drugs that can help people with rare diseases and advance clinical trials for the most promising candidates.

"No one is responsible for ensuring that drugs are fully utilized for all diseases they can help," Fajgenbaum told *USA Today*. "We're taking on that responsibility."

Repurposing existing drugs, the use of a drug approved for one indication to treat another, offers a fast way to identify drugs known to be safe that could provide benefit in other conditions. Unfortunately, it is often not in the interest of a drug company to make the effort to find additional conditions a drug may benefit, particular if the indication is rare and the drug is no longer protected by patents.

"Systemic barriers impede repurposing, so patients suffer while potential treatments are not fully utilized," Every Cure said on its website. "We overcome these barriers to systematically identify and advance promising repurposing opportunities and save lives."

"No one is responsible for ensuring that drugs are fully utilized for all diseases they can help. We're taking on that responsibility."

— David Fajgenbaum

Fajgenbaum was lying in a hospital bed dying when the drug that saved his life was available at a local pharmacy that had been approved for 50 years. The problem, the organization said, is that there have been no systemic efforts to unlock the full potential of approved drugs across diseases.

Though many diseases share common mechanisms and can benefit from the same drugs, the estimated 3,000 FDA-approved treatments are only approved for about 3,000 human diseases. Another roughly 9,000 diseases affecting millions of people do not have any approved treatments.

Today it takes about $1 billion to $2 billion and up to 15 years to develop a single, new FDA-approved drug. Repurposing safe, widely available drugs for new indications is faster and less expensive, with the greatest return on investment for saving lives.

In addition to the drug that saved Fajgenbaum's life and many other people who have Castleman disease, Every Cure says its team has identified nine other CD treatments, as well as treatments for cancer and COVID-19, including guiding the selection of drugs for the groundbreaking ACTIV-6 clinical trial. The group notes that dexamethasone and tocilizumab, which were rapidly repurposed as treatments for COVID-19, have likely saved the most lives during this pandemic.

Every Cure uses an artificial intelligence engine to identify the most promising drug repurposing opportunities. It then performs what it describes as "efficient" clinical trials in new indications.

"Unfortunately, insufficient incentives, siloed data, misaligned stakeholders, and other market failures have impeded the identification of all potential uses for all drugs, especially low-cost, generic drugs," the organization said. "The incomplete utilization of existing drugs and focus on new, expensive drugs has a disproportionately negative impact on individuals in areas with reduced access to medicines."

technologies allows it to deliver to previously inaccessible tissue and cell types and effectively target the underlying genetic drivers of diseases. The company's lead clinical program is an AOC for the rare neuromuscular disease myotonic dystrophy type 1. It also advanced AOCs into the clinic for facioscapulohumeral muscular dystrophy and Duchenne muscular dystrophy in 2022.

PepGen is employing a similar strategy to target neuromuscular diseases with oligonucleotides. Instead of conjugating the oligonucleotide with antibodies, it is using peptides to get them taken up by the tissue they need to deliver the oligonucleotide in therapeutic volumes. PepGen's so-called synthetic oligonucleotides or phosphorodiamidate morpholino oligomers are conjugated with a peptide. The company said the peptide isn't necessarily targeting the tissue, but it has found that as a result of linking the peptide to the so-called PMOs, it is able to deliver greater amounts of the therapy to muscle cells, which have been traditionally difficult to reach with RNA therapies. Once delivered, the PMOs interact with RNA to block their interactions with proteins, or with specific sites.

"We're able to get the oligonucleotide into the nucleus, the center of the cell, where it needs to be, to go and mediate the action."

—James McArthur

PepGen's lead clinical candidate is a PMO to treat Duchenne muscular dystrophy in patients amenable to exon 51 skipping. It would follow Sarepta Therapeutics' approved RNA therapy Exondys 51 for DMD for patients amenable to exon 51 skipping, but the company is betting that it will be able to deliver its therapy much more efficiently to muscle cells than Sarepta's therapy.

"Our particular approach does not appear to be focused on a specific receptor, but instead allows increased uptake into the muscle cells and other cells, like cells in the CNS," said James McArthur, CEO of PepGen. "We don't know at this point exactly the mechanism by which it's released, what we do know is that we get more oligo into cells with this approach than with other technologies that have been described. We also know that we're able to get the oligonucleotide into the nucleus, the center of the cell, where it needs to be to go and mediate the action whether it be in DMD or myotonic dystrophy."

Beyond Gene Therapy

Gene therapy does not correct an underlying genetic defect but delivers functional copies into the cell's machinery to compensate for the presence of a faulty gene. An emerging set of new technologies, though, promise to rewrite genes within a person's genome to correct, replace, or insert genes. The growing interest in technologies to do this is evidenced by the financing and dealmaking activity in 2022.

In July 2022, gene editing medicines developer Verve Therapeutics completed an upsized public offering that raised $225 million on the heels of entering a potentially lucrative four-year research collaboration with Vertex Pharmaceuticals. Verve is developing a one-and-done gene editing medicine to treat both rare and common cardiovascular diseases. This includes an experimental therapy to treat homozygous familial hypercholesterolemia, a rare genetic disease that causes high levels of LDL cholesterol and can lead to a heart attack or stroke.

The company's lead experimental therapy VERVE-101 is a base editing medicine carried in an LNP vector to the liver. It makes a single A-to-G change at a specific site in the PCSK9 gene to disrupt production of LDL cholesterol and permanently lower levels. It began dosing patients in a phase 1 clinical study in 2022 in the United Kingdom and New Zealand and expects to have data from the study in 2023.

The four-year research collaboration with Vertex is focused on discovering and developing an *in vivo* gene editing program for an undisclosed liver disease. Vertex paid an upfront fee of $25 million to Verve and also made a $35 million equity investment in the company. Verve is eligible to receive up to $66 million in success payments and $340 million in development and commercial milestones, as well as tiered royalties on future net sales for any products that result from the collaboration.

Vertex was not the only commercial therapeutics company looking to gain access to gene editing technology. Novartis Pharma entered into an exclusive worldwide *in vivo* gene editing research

and development collaboration and license agreement with Precision Biosciences to develop a one-time treatment for hemoglobinopathies such as sickle cell disease and beta thalassemia. Precision Biosciences will develop an *in vivo* gene editing medicine as a potential, one-time treatment option for diseases including certain rare blood disorders, such as sickle cell disease and beta thalassemia, using its ARCUS technology.

"The *in vivo* gene editing approach that we are pursuing for sickle cell disease could have a number of significant advantages over other *ex vivo* gene therapies currently in development," said Derek Jantz, chief scientific officer and co-founder of Precision BioSciences. "Perhaps most importantly, it could open the door to treating patients in geographies where stem cell transplant is not a realistic option."[10]

ARCUS uses a naturally occurring genome editing enzyme that evolved in a species of algae. The enzyme is a so-called homing endonuclease or meganuclease. It allows for specific cuts and DNA insertions in cellular DNA. The company believes it represents a safer and more precise way to edit genes because it is only active at its target site. It can be used to perform complex edits including gene deletions, gene repairs, and gene insertions. ARCUS can be used to insert a healthy copy of a gene at its usual site within the genome to replace a mutated, disease-causing copy. Alternatively, ARCUS can be used to insert a healthy copy of the gene at another site within the genome called a "safe harbor" that enables production of the healthy gene product without otherwise affecting the patient's DNA gene expression patterns. It is small—one-fifth the size of CRISPR Cas9 and can be delivered through virtually any delivery strategy.

Under the terms of the agreement, Novartis made a $75 million upfront payment to Precision, and is eligible to receive up to an aggregate amount of approximately $1.4 billion in additional payments based on achievement of future milestones. Precision is also eligible to receive certain research funding. If Novartis successfully commercializes a therapy from the collaboration, Precision will receive tiered royalties ranging from the mid-single digits to low-double digits on product sales.

In April 2022, Tessera Therapeutics completed a more than $300 million series C round to advance its Gene Writing platform. The company said its platform technology has the potential to cure nearly any genetic disease. It is based on mobile genetic elements (MGEs), which it said allows it to overcome limitations of existing genetic medicines. The Gene Writing technology

"It could open the door to treating patients in geographies where stem cell transplant is not a realistic option."

— Derek Jantz

can be used to make small insertions and deletions, as well as write entire genes into the genome with the delivery of only RNA. MGEs evolved to write new sequences of DNA into the genome, and Tessera has designed, built, and tested tens of thousands of engineered and synthetic MGEs to create programmable gene writing systems it said can write and rewrite the genome with efficiency, specificity, and fidelity.

While a large number of companies are pursuing strategies to alter genes within the genome, Epic Bio is developing a new class of genetic medicines that modulate gene expression. Epic Bio launched in July 2022 with $55 million in funding. Founded by CRISPR co-inventor of the University of California patent Lei Qi, the company has developed the Gene Expression Modulation System (GEMS) platform to modify gene expression with precision. Its platform technology allows it to design guide RNA that are highly specific to targeted genes. The company is using CasMINI, a Cas protein it licensed from Stanford University, which allows it to deliver its therapies *in vivo* through an AAV to a wide range or organs. The funding will be used to advance the company's preclinical programs

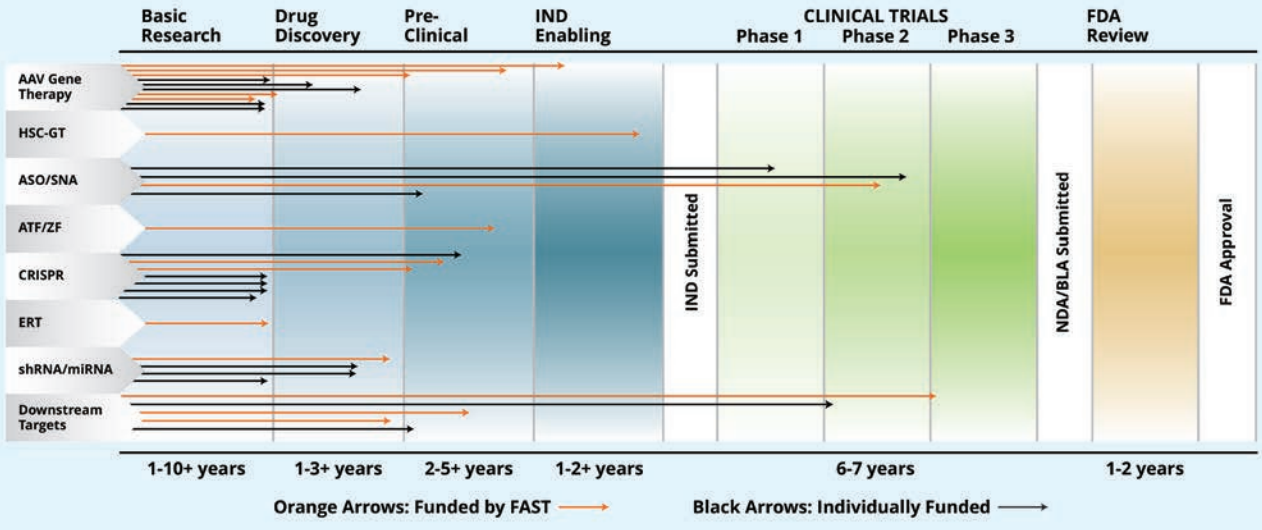
Exercise of Option Points to One Patient Foundation's Success at Building a Therapeutic Pipeline

Patient organizations are playing an increasingly active role in drug development, not satisfied with relying on drug companies to take the initiative to pursue translational research and advance potential therapies in the clinic on their own.

Consider GeneTx, a company that the Foundation for Angelman Syndrome Therapeutics (FAST) founded in 2018 to develop an experimental antisense oligonucleotide therapy to treat the rare, neurogenetic disorder Angelman syndrome.

Angelman syndrome leads to developmental delay, balance issues, motor impairment and debilitating seizures. In 2022, Ultragenyx exercised its option to acquire GeneTx for an upfront payment of $75 million plus future milestone and royalty payments.

The Angelman Syndrome Therapeutic Pipeline



Source: Foundation for Angelman Syndrome

in five initial indications including facioscapulohumeral muscular dystrophy, heterozygous familial hypercholesterolemia, alpha-1 antitrypsin deficiency, retinitis pigmentosa 4, and retinitis pigmentosa 11—as well as the ongoing development of the company's platform and discovery efforts.

Despite the significant investment and dealmaking activity into genetic medicines, it is still early in their evolution. They do represent a logical approach to treating genetic diseases and have the potential to correct a mutant gene or genetic deficit and elegantly address a disease. In addition to the technical challenges of delivering these therapies to where they need to go, there are additional obstacles, which include how to price these therapies, how to value them, and who will pay for them. At a time when it is possible to rapidly develop genetic medicines for ultra-rare patient populations in patient-led efforts, there are more complex regulatory and payment issues that emerge, particularly with regards to what level of evidence is needed and what it will take to get payers to recognize the importance of these life-saving medicines and create reimbursement mechanisms for them. ■


John Schlueter

The exercise of the option came as the two companies reported encouraging interim data of their experimental therapy GTX-102. Ultragenyx acquired the option in 2019 for $20 million. During the option period, the two companies collaborated on the development of the therapy.

GTX-102 is an antisense oligonucleotide designed to inhibit expression of UBE3A-AS. Studies show that GTX-102 reduces the levels of UBE3A-AS and reactivates expression of the paternal UBE3A allele in neurons, and that reactivation of paternal UBE3A expression in animal models of Angelman syndrome improves some of the neurological symptoms associated with the condition.

"What happened today is why FAST was founded, why we started GeneTx, and why we donate and fundraise: To discover and accelerate promising therapies for AS," said John Schlueter, chairperson of the board of FAST. "Our approach, from funding frontline discoveries through preclinical studies, to forging strategic partnerships in the biotechnology industry, aims to quickly advance translational research, so that families living with AS move closer to potentially transformative treatments."

GeneTx is just one part of a broader strategy the foundation embarked on to develop a cure for Angelman syndrome. In 2013, it assembled and funded a team of five academic laboratories that have worked collaboratively on research and then in 2015 brought in a chief scientific officer to develop a "roadmap to a cure."

The foundation has funded 15 therapies in development across seven therapeutic modalities. This includes three gene therapies in preclinical development and two CRISPR therapies in preclinical development.

A Down Year for Drug Approvals

"One fortunate aspect of working in rare disease policy is that both Democrats and Republicans agree on the need to get more treatments to rare disease patients. There's a lot of consensus about that."

— Amanda Malakoff, executive director of the Rare Disease Company Coalition, an industry advocacy group

The effects of the COVID-19 pandemic, the war in Ukraine, and the subsequent economic downturn have caused drug developers to trim their pipelines and focus on programs with near-term and best chances for success. Perhaps the best indicator of the long-term impact these developments will have on bringing new therapies to rare disease patients, albeit a lagging one, will be the number of novel therapies approved by the U.S. Food and Drug Administration. It may be years, if ever, that such manifestations may be seen. It's unclear whether any of these factors weighed on drug approvals in 2022, but it was a down year for FDA approvals of novel therapies.

The FDA's Center for Drug Evaluation and Research approved 20 novel therapies for rare disease in 2022, 54 percent of the 37 novel drugs the division approved in 2022. That represented a 23 percent decline in the number of novel orphan drugs approved compared to the 26 the agency approved the previous year. It was the second year of decline in novel rare disease drug approvals. A total of nine of the novel orphan drug approvals, 45 percent, were for medicines to treat rare cancers.

Of the 20 novel rare disease drug approvals in 2022, 12 were first-in-class therapies, nine had Breakthrough Therapy designation, and 14 benefited from Priority Review. Six of the therapies won approval through the accelerated approval pathway.

Despite the overall decline, the agency did make notable approvals in 2022. Amylyx Pharmaceuticals' won approval for Relyvrio, an oral combination therapy for the rare, neurodegenerative disease amyotrophic lateral sclerosis, a progressive and fatal neurodegenerative disorder caused by motor neuron death in the brain and spinal cord. Motor neuron loss in ALS leads to deteriorating muscle function, the inability to move and speak, respiratory paralysis, and eventually, death.

"Any time we have a new tool to slow the progression of this disease represents an important milestone in how we battle ALS," said Sabrina Paganoni, principal investigator of the CENTAUR trial, investigator at the Sean M. Healey and AMG Center for ALS at Massachusetts General Hospital, and associate professor of Physical Medicine and Rehabilitation at Harvard Medical School and Spaulding Rehabilitation Hospital. "The published data on both

function and survival in a randomized trial—and what this means for people living with ALS—are a step forward for the ALS community."

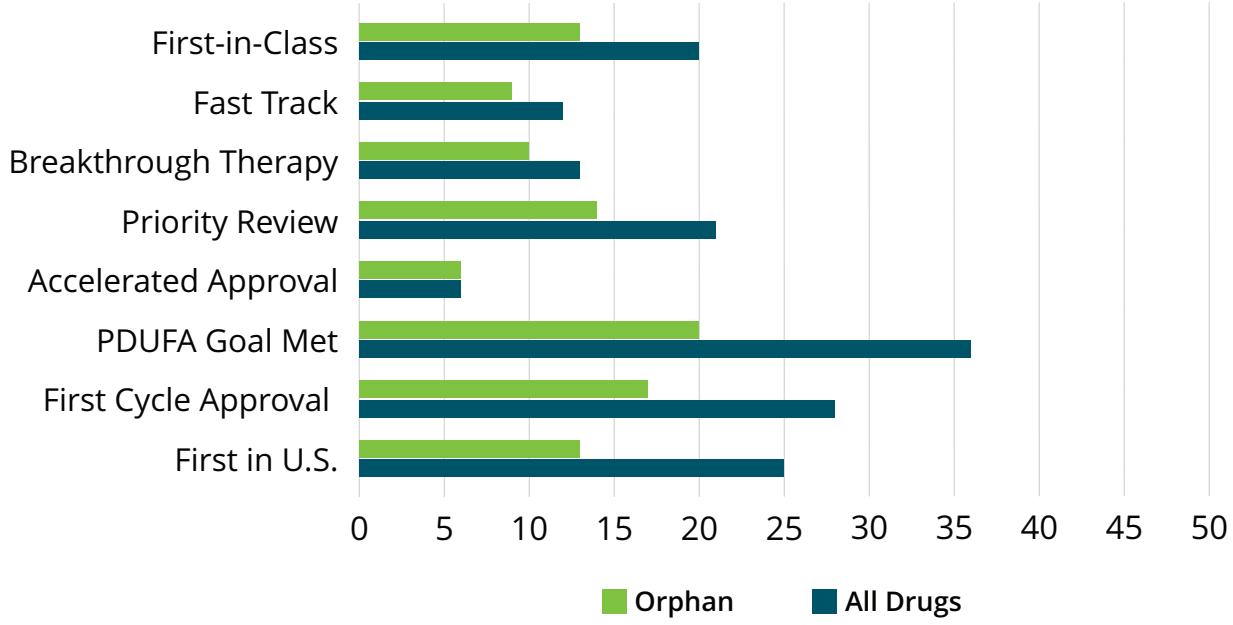
The FDA's Center for Biologics Evaluation and Research also made a number of significant approvals in 2022 with three gene therapies all getting a greenlight. In August 2022, Bluebird Bio won approval for Zynteglo, a one-time gene therapy to treat the underlying genetic cause of beta thalassemia in adult and pediatric patients who require regular red blood cell transfusions. With 1,300 to 1,500 people with transfusion-dependent beta thalassemia in the United States, Bluebird was expected to charge $2.8 million for the therapy, making it the most expensive medicine on the market.

The company said the pricing reflected the "robust and sustained clinical benefit" shown in clinical studies and its potential to relieve "a lifetime" of healthcare costs associated with transfusions and iron management. Bluebird noted that the lifetime medical care cost for patients with transfusion-dependent beta-thalassemia can reach $6.4 million.[11]

Zynteglo had won approval in Europe in 2019, where the company had priced it at just $1.8 million. Nevertheless, Bluebird pulled the therapy from the market because it could not get payers there to recognize the value of the therapy at that price. It also pulled a second gene therapy from Europe and shut down its European operations saying that "European payers have not yet evolved their approach to gene therapy in a way that can recognize the innovation and the expected life-long benefit of these products."[12]

Beta thalassemia is a rare, genetic blood disease caused by a mutation that results in the inability of people with the condition to produce adequate amounts of hemoglobin, the protein that carries oxygen in red blood cells. Patients with transfusion-dependent beta thalassemia suffer from anemia and require regular red blood cell transfusions throughout their lives, a lengthy process that patients typically undergo every two to five weeks. These patients suffer the risk of iron overload from these treatments, which has been associated with a shortened lifespan. Cooley's Anemia Foundation found that the median age of death of patients with

U.S. Food and Drug Administration Novel Drug Approvals in 2022 by Designation



Source: U.S. Food and Drug Administration

transfusion-dependent beta thalassemia in the United States who died during the last decade was just 37 years.

Though Zynteglo is intended to be a one-and-done gene therapy, it requires a several months process to prepare the customized therapy. Blood forming hematopoietic stem cells are taken from the patient and then modified to have functional copies of the beta-globin gene inserted with a lentiviral vector while the cells are outside the body. The patient is then infused with the cells in a single treatment to allow them to make hemoglobin without regular red blood cell transfusions.

In two, single-arm, open label phase 3 studies and a long-term follow-up study that included 41 patients ranging in age from 4 to 34 who were followed for up to four years, 89 percent of the evaluable patients achieved transfusion independence. The most common non-laboratory adverse reactions were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. The most common Grade 3 or 4 laboratory abnormalities (>50 percent) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.


Andrew Obenshain

"As the first *ex vivo* lentiviral vector gene therapy approved in the U.S. for the treatment of people with beta thalassemia, we are ushering in a new era in which gene therapy has the potential to transform existing treatment paradigms for diseases that currently carry a lifelong burden of care," Bluebird Bio CEO Andrew Obenshain said in announcing the approval.

Zynteglo was in good company. In 2022, a slate of new gene therapies reached the market in the United States and Europe with critical approvals for Bluebird Bio, CSL Behring, BioMarin, and PTC Therapeutics. The move to the market is providing hope that a growing number of patients with genetic diseases would benefit from these emerging therapies. While concerns about safety, durability, and the ability to target specific cells within the body (as well as pricing concerns) remain barriers to expanding access to these therapies, innovative approaches to overcoming these hurdles promise to expand the availability of functionally curative medicines.

A month after Bluebird Bio won FDA approval for Zynteglo, the FDA approved the company's separate gene therapy, Skysona, to treat the progressive neurodegenerative condition early, active cerebral adrenoleukodystrophy. The approval was made under the agency's accelerated approval pathway. Skysona will have a wholesale price of $3 million, eclipsing the price of Zynteglo.

As a condition of the Skysona accelerated approval, Bluebird has agreed to provide confirmatory, long-term clinical data to the FDA. Bluebird anticipates that this will include data from the ongoing long-term follow-up study, which follows patients treated in clinical trials for 15 years, and from commercially treated patients. The gene therapy will be available through a limited number of qualified treatment centers in the United States.

Cerebral adrenoleukodystrophy (CALD) primarily affects young boys and causes irreversible neurologic decline, including major functional disabilities. These can include loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. Nearly half of patients who do not receive treatment die within five years of symptom onset. Prior to the approval of Skysona, effective options were limited to allogeneic hematopoietic stem cell transplant, which is associated with the risk of potential, serious complications including death, which can increase dramatically in patients without a human leukocyte antigen matched donor.

Skysona is a one-time gene therapy custom-designed to treat the underlying cause of CALD. Skysona uses *ex vivo* transduction with the Lenti-D lentiviral vector to add functional

U.S. FDA 2022 Biological License Application Approvals for Orphan Indications

Approval Date	Trade Name	Manufacturer	Indication
2/28/2022	Carvykti	Janssen Biotech	Indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
8/17/2022	Zynteglo	Bluebird Bio	Indicated for the treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell (RBC) transfusions.
9/16/2022	Skysona	Bluebird Bio	Indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD).
11/22/2022	Hemgenix	CSL Behring	Indicated for treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.
11/30/2022	Rebyota	Ferring Pharmaceuticals	Indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Source: U.S. Food and Drug Administration

copies of the ABCD1 gene into a patient's own hematopoietic stem cells. The addition of the functional ABCD1 gene allows patients to produce the ALD protein, which can then participate in the local degradation of very long-chain fatty acids. This degradation of VLCFAs is believed to slow or possibly prevent further inflammation and demyelination.

The approval of Skysona was based on data from Bluebird Bio's phase 2/3 study ALD-102 (Starbeam) and phase 3 ALD-104 study. Both open-label, single-arm studies enrolled patients with early, active CALD who had elevated very long chain fatty acid values, a Loes score between 0.5 and 9 (inclusive), and gadolinium enhancement on magnetic resonance imaging of demyelinating lesions. Additionally, patients were required to have a neurologic function score of ≤ 1, indicating limited changes in neurologic function. The efficacy of Skysona was compared to a natural history population.

Bluebird Bio's two approvals were followed in November with the FDA granting approval to CSL Behring's Hemgenix, for the first gene therapy to treat hemophilia B, a rare bleeding disorder. Hemophilia B represents about 15 percent of patients with hemophilia. Patients with the severe form of the condition typically require a routine treatment regimen of intravenous infusions of factor IX replacement products to maintain sufficient levels of clotting factor to prevent bleeding episodes.

Hemgenix is a one-time gene therapy product given as a single dose by IV infusion. Hemgenix consists of a viral vector carrying a gene for clotting Factor IX. The gene is expressed in the liver to produce factor IX protein, to increase blood levels of factor IX and thereby limit bleeding episodes. It received Priority Review, Orphan, and Breakthrough Therapy designations. CSL expected to set the price of the therapy at $3.5 million.

While three gene therapies won approval in the United States in 2022, PTC Therapeutics and BioMarin each had gene therapy successes in Europe. In July 2022, the European Commission granted marketing authorization to PTC Therapeutics for Upstaza, its gene therapy for the rare and fatal disorder aromatic L-amino acid decarboxylase (AADC) deficiency. It is the first marketed gene therapy directly infused into the brain. The European Commission approved Upstaza for people with AADC 18 months and older. The marketing authorization covers all 27 European Union member states, as well as Iceland, Norway, and Liechtenstein.

FDA's Marks Calls for Greater Focus on Translational Science for Gene Therapies

Gene therapies, like small molecule drugs, need to be shown to be safe and effective in order to gain regulatory approval. But there are notable differences between these therapeutic modalities.

Peter Marks, the U.S. Food and Drug Administration regulator who oversees the division responsible for gene therapies, raised questions about whether the pace of development of gene therapies has been slowed by applying a framework to these genetic medicines that was developed for traditional therapies.

In an editorial in the journal *Expert Opinion on Biological Therapy*, the director of the FDA's Center for Biologics Evaluation and Research argued that greater attention needs to be paid to how to translate scientific advances into practical ones that can benefit people to fully realize the potential of gene therapies.[13]

Marks said there are aspects of the framework for the clinical development of small molecule drugs that can be appropriately applied to the development of gene therapies, such as understanding the non-clinical aspects of the product, the use of good manufacturing practices, and the demonstration of safety and efficacy.

But there are other aspects of gene therapies that may be better suited for different models. For instance, Marks noted that gene therapies use a vector backbone to deliver a transgene. "Considering the 'device-like' quality of this vector backbone allows one to consider whether, within specific limits, one could reuse information related to the vector backbone to expedite the development of multiple gene therapy products," he wrote.

One bottleneck for the development of gene therapies today is manufacturing small batches of product. Often gene therapies originate in academic labs or small companies, which have adequate capabilities to produce material for clinical trials. But when these products are transferred to contract manufacturers who produce materials in accordance with good clinical manufacturing practices, it can be expensive and time consuming. He suggests this could be addressed by standardizing processes and reusing well-characterized gene therapy vectors to streamline the movement from one gene therapy to another to address different diseases.

Other points Marks touched on included advances in the use of novel endpoints and clinical trial designs, enhanced communication with regulatory authorities, and harmonization of global regulations, all of which could accelerate the availability of these therapies.

"There has been tremendous scientific progress in the gene therapy field over the past two decades. The introduction of genome editing has further catapulted the field forward," he wrote. "However, greater attention needs to be focused now on translating these scientific advances into practical ones that can improve people's lives. Though it may not be an easy task, it is certain to be rewarding to those in need of safe and effective treatments and our society."

"Greater attention needs to be focused now on translating these scientific advances into practical ones that can improve people's lives."

—Peter Marks

AADC deficiency typically causes severe disability and suffering from the first months of life, affecting every aspect of life—physical, mental, and behavioral. The suffering of children with AADC deficiency may be exacerbated by episodes of distressing seizure-like oculogyric crises that cause the eyes to roll up in the head, frequent vomiting, behavioral problems, and difficulty sleeping. The lives of affected children are severely impacted and shortened. Ongoing physical, occupational, and speech therapy, and interventions, including surgery, also are often required to manage potentially life-threatening complications such as infections and severe feeding and breathing problems.

Upstaza is a one-time gene replacement therapy that delivers a functional copy of the DDC gene through an AAV2 vector. Upstaza is delivered directly to the putamen, a part of the brain involved in learning and motor control. The therapy increases the AADC enzyme and restores dopamine production. In clinical studies, patients, not achieving any developmental motor milestones, when treated with Upstaza achieved clinically meaningful motor skills from as early as three months following treatment with improvements shown to continue up to ten years after treatment. Cognitive skills improved in all treated patients. Treatment also reduced symptoms that cause potentially life-threatening and morbid complications.

BioMarin Pharmaceutical also won European approval for Roctavian, its gene therapy to treat hemophilia A. The one-time infusion is for adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5), which is used as the vector for the therapy.

Hemophilia A is an X-linked genetic disorder caused by missing or defective factor VIII, a clotting protein. People living with hemophilia A lack sufficient functioning Factor VIII protein to help their blood clot and are at risk for painful and/or potentially life-threatening bleeds from even modest injuries. About half of the people with hemophilia A have the severe form of the disease and often experience painful, spontaneous bleeds into their muscles or joints.

People with hemophilia A have long relied on a prophylactic regimen of replacement factor VIII infusions administered intravenously two to three times a week. Even with such treatment, many people continue to experience breakthrough bleeds, resulting in progressive and debilitating joint damage, which can have a major impact on their quality of life. Roctavian delivers a functional gene that is designed to enable the body to produce factor VIII on its own with the goal of reducing the need for factor VIII injections.

In August 2020, the FDA notified the company it would not approve the gene therapy without additional data to demonstrate its durability. The concern was that even though all of the participants in an open-label phase 1/2 study of the gene therapy remained off prophylactic therapy after a single dose, the data also showed that factor VIII activity levels declined with the most recent years' data, even though the participants maintained high enough levels of factor VIII to prevent spontaneous bleeding events. The agency said it wanted to see two years of data from the phase 3 study to provide substantial evidence of a durable effect using annualized bleeding rate, the endpoint of the study. BioMarin resubmitted Roctavian to the FDA at the end of September 2022.

Unfinished Work

The reauthorization of the Prescription Drug User Fee Act, legislation that assures drug developers that the U.S. Food and Drug Administration will provide timely action on new drug applications in exchange for user fees to fund the work, passed at the end of September 2022. It was the seventh incarnation of the act known as PDUFA. As in the past, the legislation was renewed for a five-year period. But unlike previous versions, which have become fertile ground for both the drug industry and its critics to attach riders, the version of PDUFA VII that passed was a far more slimmed down version than has become the custom. It left a set of related bills for the lame duck session of Congress to consider.

PDUFA VII included the establishment of the Rare Disease Endpoint Advancement pilot, a joint program of the FDA's Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, designed to support novel efficacy endpoint development for drugs that treat rare diseases. It creates a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process. The agency will also develop staff capacity to facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

The legislation also called for the FDA to establish the Split Real Time Application Review, or STAR, pilot program. The STAR program is designed to shorten the time from the date of complete submission to the action date, to allow earlier patient access to therapies that address an unmet medical need.

Finally, PDUFA VII instructed the FDA to create the Advancing Real-World Evidence program, which is intended to improve the quality and acceptability of real-world evidence-based approaches to support. Trial sponsors selected

Uncertainty and Inaction in the Wake of a Court Ruling on Orphan Drug Exclusivity

At the end of September 2021, the U.S. Court of Appeals for the 11th Circuit overturned a lower court ruling in the case of Catalyst Pharms., Inc. v. Becerra, a decision that the U.S. Food and Drug Administration expects to affect the incentives for research and development of medical products for rare diseases.

In June 2019, Catalyst filed a lawsuit against the FDA calling for it to withdraw its approval of the Jacobus drug Ruzurgi for the treatment of Lambert-Eaton Myasthenic syndrome, or LEMS, in pediatric patients. LEMS is a rare autoimmune condition in which the body attacks the junction between nerves and muscles.

Catalyst won FDA approval for its drug Firdapse in late 2018 to treat adults with LEMS and set the annual list price of the drug at $375,000. The FDA then approved Jacobus Pharmaceutical's Ruzurgi for pediatric patients age 6 to 16. Both Firdapse and Ruzurgi are amifampridine and Catalyst charged that in approving for Firdapse. While a drug approved for pediatric use can be prescribed off-label for adults, a drug approved for adult use cannot be prescribed for pediatric patients under the Orphan Drug Act as well as other provisions.

More than 60 products approved for more than 70 orphan designated indications have gone with no determination of orphan exclusivity.

Jacobus' drug, it violated its right to orphan drug exclusivity (ODE), which prohibits the FDA from approving the same drug for the same indication for a period of seven years.

Jacobus priced its LEMS pill at just under half the cost of a similar dosage of Catalyst's pill. Catalyst charged that the FDA's approval of Ruzurgi was an illegal regulatory workaround of its seven years of exclusivity

Catalyst brought suit against the FDA saying the agency illegally approved Ruzurgi, but a U.S. district court dismissed the suit in October 2020 saying that the phrase in the statute "same disease or condition" was ambiguous. A year later, The Appeals Court said the district court erred in its determination that the phrase is ambiguous and said it is not supported by the statutory text.

to participate in the program can meet with agency staff prior to protocol development or the start of a study to discuss the use of real-world evidence in their product development.

Congress left for year-end consideration a spate of bills of importance to the rare disease community. This included the HEART Act (an effort to ensure the FDA use rare diseases experts on advisory committee panels for rare disease drugs and that members of the patient community be consulted on Risk Evaluation and Mitigation Strategies), STAT Act (which would create a rare disease center of excellence within FDA, support the development of drugs to treat ultra-rare diseases, and improve patient access to therapies), as well as efforts to address the feared weakening of FDA's accelerated approval pathway, which has been a critical tool for getting rare disease therapies to market.

In the end, while those bills didn't pass, Congress did incorporate elements from them in a $1.7 trillion spending bill approved at the end of the year to fund government operations

"The FDA's approval of Ruzurgi was contrary to the unambiguous language of the Orphan Drug Act. Catalyst Pharmaceuticals, Inc., held the exclusive right to market, Firdapse, an orphan drug, for a period of seven years in order to treat the rare autoimmune disease, LEMS," wrote Judge Barbara Lagoa of the 11th Circuit Court of Appeals in her ruling. "Because it is undisputed that none of the statutory exceptions to Catalyst's market exclusivity apply, the FDA was prohibited from approving for sale the same drug manufactured by Jacobus Pharmaceutical Company, Inc., to treat the same autoimmune disease during the period of Catalyst's market exclusivity. As a result, the FDA's action was arbitrary, capricious, and not in accordance with law, and its approval of Ruzurgi must be set aside."

The FDA, though, has expressed concerns about the long-term effects of the ruling. In a post to its website, the agency said under the Catalyst decision, the first company to gain approval for any use for a drug that has been designated for a rare disease will, in most cases, have seven years of exclusivity for its drug for the entire rare disease. The agency had taken the approach that orphan drug exclusivity could be granted for narrower use or indication than an entire disease.

"The Catalyst decision adversely resolves a statutory issue about the scope of ODE. The Catalyst decision interpreted the Orphan Drug Act to unambiguously tie ODE to the disease or condition for which the drug was designated, which would leave the FDA with no discretion to address the issue differently," the agency wrote on its website in May 2022. "In the coming months, the FDA will need to consider how the decision affects drugs with active terms of orphan drug exclusivity as well as currently marketed drugs, including generics. Going forward, the FDA expects that some drugs that are in late-stage development, or that have already been submitted for marketing application review, would be blocked from approval under the Catalyst decision's interpretation of the Act."[14]


FDA Commissioner Robert Calif

The FDA published a notification in the Federal Register in January 2023 that said it will comply with the federal court's ruling in the Catalyst case but will continue to tie the scope of orphan drug exclusivity to the indication or uses for which a drug is approved.

"FDA believes that its statutory interpretation embodied in its regulations best advances the Orphan Drug Act's purposes, appropriately balancing the need to incentivize the development of drugs for rare diseases and conditions with the need to provide patient access to orphan drugs," the agency said.

through the end of September 2023. The omnibus appropriations bill included $6.6 billion in funding for the FDA, a $226 million increase from fiscal 2022. The funding provides the FDA with $3.5 billion discretionary funding.

The final spending bill provided reauthorization of the Orphan Products Grants Program, which grants the agency the authority to require drugmakers initiate confirmatory trials before granting accelerated approval and calls for the establishment of a council of agency officials to establish consistent policies to guide the use of accelerated approval.

The legislation calls on the FDA to produce a report on its activities relating to the development and review of rare disease drugs including what it is doing in terms of training and other efforts to ensure the expertise of personnel involved in the review of applications for therapies to treat rare diseases. The legislation calls on the agency to instruct drug developers to provide diversity action plans for late-stage clinical trials.

It includes a two-year extension for telehealth flexibilities put in place in response to the COVID-19 pandemic. This will allow continued access to telehealth services through Medicaid and Medicare. Congress also allocated funding to continue the work of the Undiagnosed Diseases Network, which seeks to find answers for patients suspected of having an undiagnosed rare disease. Finally, the bill provides funding for a study to make recommendations on how to improve newborn screening.

Fears of Gridlock

The year-end spending bill may have been the best chance for rare disease advocates to see legislation they champion passed for the next two years. While rare disease issues transcend party politics, the mid-term election results gave a slim majority to the Democrats in the Senate and a narrow majority to the Republicans in the House. The divided legislature is expected to be a contentious and difficult environment in which to advance legislation.

Among the top priorities for rare disease drugmakers in the new legislative session will be to restore the Orphan Drug Tax Credit back to 50 percent for clinical testing expenses for rare diseases. The Trump administration's Tax Cut and Jobs Act in 2017 cut the tax benefit to 25 percent. Josh Gottheimer, a New Jersey Democrat, first introduced legislation to restore the tax credit to its original level in 2020. The legislation, known as Cameron's Law, is named for a New Jersey boy with the rare lysosomal storage disorder San Filippo Syndrome. Republican Fred Upton co-sponsored the legislation. Though Upton is retiring from Congress, Gottheimer won re-election, which is providing hope to the industry that he will reintroduce the legislation in the new session of Congress.

"We see Democrats and Republicans working across the aisle on rare disease policy issues," said Amanda Malakoff, executive director of the Rare Disease Company Coalition, an industry advocacy group. "We are remaining optimistic and hopeful that that bipartisan work will continue. One fortunate aspect of working in rare disease policy is that both Democrats and Republicans agree on the need to get more treatments to rare disease patients. There's a lot of consensus about that." ■

U.S. Food and Drug Administration Orphan Drug Approvals in 2022

Proprietary Name	Active Ingredient	Indication	Approval Date	Designations
Amvuttra	vutrisiran	To treat polyneuropathy of hereditary transthyretin-mediated amyloidosis	6/13/2022	
Camzyos	mavacamten	To treat certain classes of obstructive hypertrophic cardiomyopathy	4/28/2022	
Elahere	mirvetuximab soravtansine-gynx	To treat patients with recurrent ovarian cancer that is resistant to platinum therapy	11/14/2022	
Enjaymo	sutimlimab-jome	To decrease the need for red blood cell transfusion due to hemolysis in cold agglutinin disease	2/4/2022	
Imjudo	tremelimumab	To treat unresectable hepatocellular carcinoma	10/21/2022	
Kimmtrak	tebentafusp-tebn	To treat unresectable or metastatic uveal melanoma	1/25/2022	
Krazati	adagrasib	To treat KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer in adults who have received at least one prior systemic therapy	12/12/2022	
Lunsumio	mosunetuzumab-axgb	To treat adults with relapsed or refractory follicular lymphoma, a type of non-Hodgkin lymphoma	12/22/2022	
Lytgobi	futibatinib	To treat intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements	9/30/2022	
NexoBrid	anacaulase-bcdb	To remove eschar in adults with deep partial thickness or full thickness thermal burns	12/28/2022	
Opdualag	nivolumab and relatlimab-rmbw	To treat unresectable or metastatic melanoma	3/18/2022	
Pyrukynd	mitapivat	To treat hemolytic anemia in pyruvate kinase deficiency	2/17/2022	
Relyvrio	sodium phenylbutyrate/ taurursodiol	To treat amyotrophic lateral sclerosis (ALS)	9/29/2022	
Rezlidhia	olutasidenib	To treat adults with relapsed or refractory acute myeloid leukemia with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation	12/1/2022	
Spevigo	spesolimab-sbzo	To treat generalized pustular psoriasis flares	9/1/2022	
Tecvayli	teclistamab-cqyv	To treat relapsed or refractory multiple myeloma among adults who have received at least four specific lines of therapy	10/25/2022	
Terlivaz	terlipressin	To improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function	9/14/2022	
Vonjo	pacritinib	To treat intermediate or high-risk primary or secondary myelofibrosis in adults with low platelets	2/28/2022	
Xenpozyme	Olipudase alfa	To treat Acid Sphingomyelinase Deficiency	8/31/2022	
Ztalmy	ganaxolone	To treat seizures in cyclin-dependent kinase-like 5 deficiency disorder	3/18/2022	

Source: U.S. Food and Drug Administration

The Global Economy Weighs on Rare Disease Drug Development

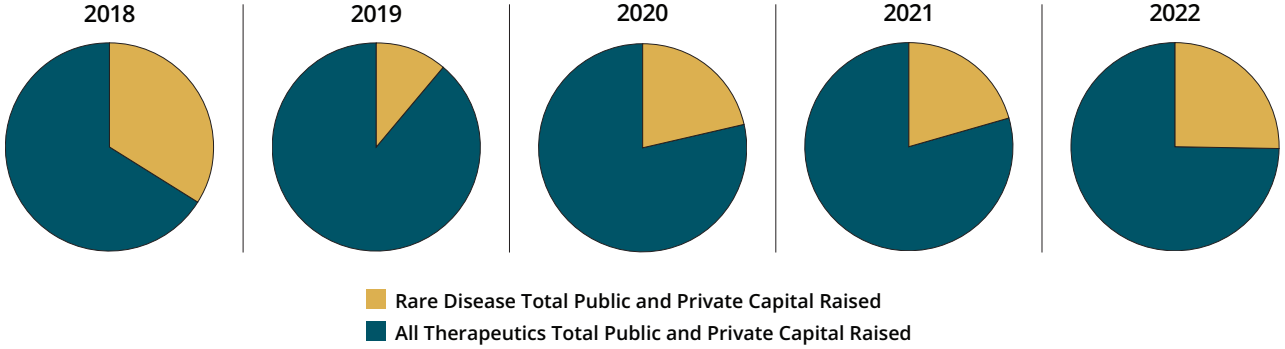
The public market sell-off that hit biotechnology stocks in 2021 continued throughout 2022 as Russia's invasion of Ukraine, inflation, and the Federal Reserve Bank's interest rate hikes to curb rising prices kept pressure on stocks and dampened financing for the sector. Though venture investors had plenty of capital to deploy, they remained selective and clinical developments grew ever more important to the financial fate of rare disease drug developers.

These companies grew opportunistic and turned to capital markets to raise money in the wake of good news or moved with speed to cut spending and staff when clinical results disappointed. The rare disease sector saw 40 companies announce restructurings with nine of them cutting more than half their staffs, and three—Escape Bio, Triplet Therapeutics, and Sio Gene Therapies—shut down operations.

To consider that rapid turn in fortunes for companies raising money, consider Sio, previously known as Axovant. It raised $315 million in a 2015 IPO, and an additional $129.7 million in 2020. The company faltered after a late-stage failure of its experimental therapy for Alzheimer's disease. The company renamed itself Sio Gene Therapies and shifted its focus to gene therapies for conditions of the central nervous system. The company was developing gene therapies for GM1 gangliosidosis and Tay-Sachs/Sanhoff disease.

"After a thorough review of our ongoing programs, and given the current public financing environment, we have decided to terminate our GM1 and GM2 licensing agreements with UMass and wind down our related clinical trials and manufacturing operations," David Nassif, CEO of Sio, said in a statement in December 2022.

Rare Disease Total Financings as a Percent of All Therapeutics 2018 to 2022



Source: DealForma and Global Genes

Rare Disease Company Layoffs and Restructurings in 2022

Date	Company	Size of Cut	Trigger
3/1/2022	Epizyme	12%	Reduced its clinical trials to conserve cash
3/11/2022	Orphayzme	50%	Lead program in inclusion body myositis failed in phase 2/3 study and company begins in-court restructuring
3/15/2022	Ovid Therapeutics	20%	Company made the cuts as its focuses on late-stage therapies for rare epilepsies
3/15/2022	BridgeBio Pharma	Unknown	Company initiated a restructuring following a phase 3 failure of ATTR therapy
3/15/2022	Passage Bio	13%	Cuts come as company seeks to extend its cash runway
3/31/2022	Catalyst Biosciences	70%	Company working to close down
3/31/2022	Orchard Therapeutics	30%	Cutting cost to focus on Libmeldy, its gene therapy for early-onset leukodystrophy approved in Europe and expected to be submitted to the FDA in 2022
4/1/2022	Taysha Gene Therapies	35%	Narrows its R&D efforts to focus on advancing its GAN and Rett syndrome gene therapy programs to pivotal studies
4/5/2022	Bluebird Bio	30%	Cuts follow setbacks in Europe to reduce cash burn
4/7/2022	Akcea (Ionis)	70%	Akcea, which is now part of Ionis, made the cuts following its deal with Sobi to distribute Akcea's products in Europe
4/13/2022	ProQR	30%	Follows a phase 2/3 failure of lead program
4/14/2022	Magenta Therapeutics	14%	Focusing on conditioning stem cell program and sickle cell disease
4/18/2022	Imara	83%	Phase 2B failure causes company to reduce headcount to just six employees
4/27/2022	Solid Biosciences	30%	Focuses on two DMD programs
4/27/2022	Sio Gene Therapies	Majority of staff	Terminated GM1 and GM2 gene therapy programs as it explores alternatives
4/25/2022	Saniona	All U.S. positions	Shut down U.S. operations to cut expenses by 75%
4/28/2022	SwanBio Therapeutics	25%	Cuts made after expected financing fell through
5/5/2022	Avalo Therapeutics	33%	Layoff follows steep drop in stock price and departure of key executives as company seeks to cut its burn rate
5/10/2022	Orion	37 employees	Refocuses its pipeline on cancer and pain
5/16/2022	Agios	50 employees	Cuts half its R&D staff to focus on late-stage pipeline
5/16/2022	Scholar Rock	25%	Cuts made as the company prioritizes its candidate for spinal muscular atrophy and solid tumors
6/15/2022	Praxis Precision Medicine	139 employees	Phase 2/3 failure in major depressive disorder
6/28/2022	Roivant		Cuts four programs including gene therapy for sickle cell
6/30/2022	Avadel Pharmaceuticals	50%	Prioritizes approval of narcolepsy drug and preparations for commercial launch
6/30/2022	AavantiBio	30 employees	Cuts focused on the company's CMC group
7/19/2022	Invitae	33%	The company cut 1,000 employees as part of an effort to streamline and reduce costs to save $326 million annually by 2023 and extend the company's cash runway to the end of 2024.
7/6/2022	Adverum Biotechnologies	38%	Cut headcount and expenses to focus on its lead candidate, a gene therapy for wet age-related macular degeneration and focus pipeline on highly prevalent ocular diseases.
7/21/2022	X4 Pharmaceuticals	20%	The company said it would focus on its lead experimental clinical candidate, mavorixafor, in WHIM syndrome and other chronic neutropenic disorders. The cuts followed a $55 million PIPE offering and an amendment to a $20 million loan facility to extend for up to 12 months the interest-only period on the loan.
8/15/2022	Homology Medicines	10%	Prioritized its PKU gene editing candidate HMI-103 and paused enrollment on its PKU gene therapy HMI-102 to extend runway
8/24/2022	Aeglea Therapeutics	25%	FDA sent refusal-to-file letter for pegzilarginase
9/26/2022	Exicure	66%	Halted R&D activity. Problems date back to end of 2021 report that it misreported preclinical data
10/7/2022	BioMarin Pharmaceutical	4%	The company said it laid off 120 employees to simplify the organization and create efficiencies
10/12/2022	Triplet Therapeutics	Shut down	Repeat failures of other companies' Huntington's disease trials and a slowdown in biotech financing left the company struggling to attract investors for capital to continue its operations.
10/14/2022	Neubase Therapeutics	60%	Pivot from antisense to gene editing
10/18/2022	Mereo BioPharma	40%	Focus on two rare disease programs
10/24/2022	Phase Bio	Filed Chapter 11	Pursuing an auction and sale
11/14/2022	Passage Bio	23%	Cut staff to extend its cash runway to H1 2025
11/30/2022	Sana Biotechnology	15%	Optimized the development of programs at or nearing clinical development to extend its cash runway into 2025
12/1/2022	Synlogic	25%	Cut designed to extend cash runway to second half of 2024
12/2/2022	Escape Bio	Closed	Company entered an insolvency proceeding in California
12/15/2022	Sio Gene Therapies	Liquidating	Decided to sell all assets after exploring strategic options including a possible sale

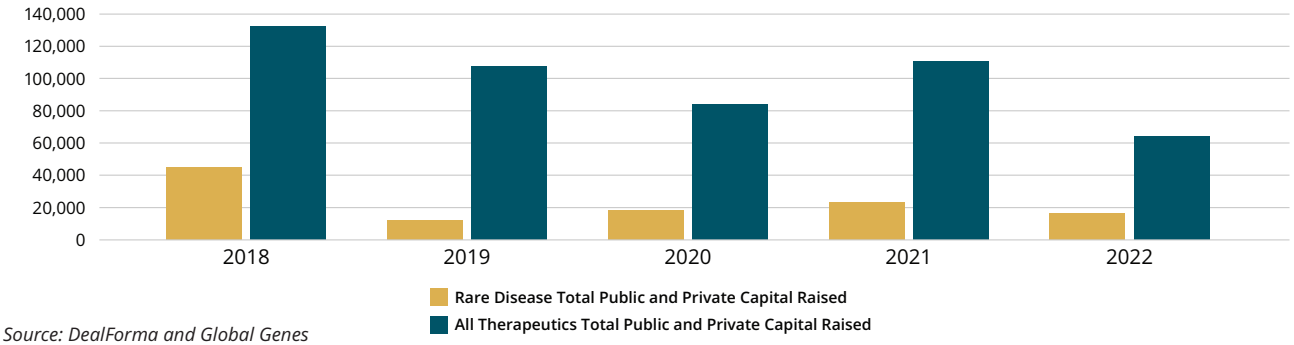
Source: Global Genes, Fierce Biotech, Endpoints, STAT

Overall, rare disease drug developers in 2022 raised a total of $16.3 billion in public and private financings, a 29 percent decline from the $22.9 billion raised in 2021, according to data from Dealforma and Global Genes. Rare disease drug developers, however, performed better than the industry as a whole as total financings for all drug developers fell 42 percent in 2022 to $64.2 billion. Overall, rare disease drug developers captured 25 percent of total industry funding in 2022 compared to 21 percent the previous year.[15]

Venture capital investment in rare disease therapeutics developers in 2022 fell to $5.2 billion, a 41 percent drop from the $8.8 billion rare disease drug developers raised for the same period a year ago. That compared to a 48 percent drop in venture financings for all drug developers in 2022 to $20.8 billion.

In the area of rare disease, gene therapy and gene editing developers captured the six largest venture financings in 2022. Overall, gene therapy and gene editing companies accounted for 38

Total Therapeutic Financings 2018-2022 (USD M)



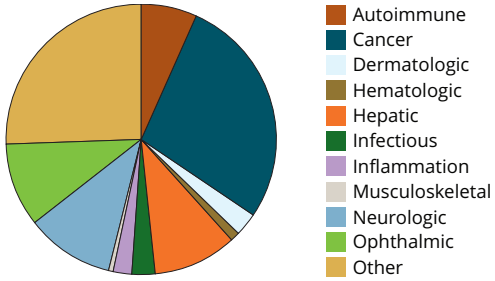
Source: DealForma and Global Genes

Capital Raised by Rare Disease Therapeutics Companies in 2022 (USD M)

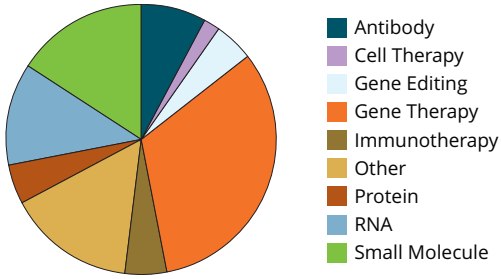
Deal Type	2022	2021	Change
Rare Disease Venture Capital	5,185	8,822	-41.23%
All Therapeutics Venture Capital	20,824	39,974	-47.91%
Rare Disease IPOs	833	4,309	-80.67%
All Therapeutics IPOs	1,668	14,969	-88.86%
Rare Disease Public Equity and Debt (excl. U.S. IPOs)	10,258	9,786	4.82%
All Therapeutics Public Equity and Debt (excl. U.S. IPOs)	41,693	55,823	-25.31%
Total Rare Disease Equity and Debt (Public and Private)	16,276	22,917	-28.98%
Total All Therapeutics Equity and Debt (Public and Private)	64,185	110,766	-42.05%
RD Partnering Deal Value at Signing	2,607	4,768	-45.32%
All Therapeutics Partnering Value at Signing	11,679	14,752	-20.83%
RD Partnering Total Potential Deal Value	42,110	59,681	-29.44%
All Therapeutics Total Potential Deal Value	169,739	158,884	6.83%
Rare Disease M&A Deal Value at Signing	50,572	49,487	2.19%
All Therapeutics M&A Deal Value at Signing	85,128	83,404	2.07%
RD M&A Total Potential Deal Value	51,854	52,620	-1.46%
All Therapeutics M&A Total Potential Deal Value	103,336	97,758	5.71%

Notes: "Rare Disease" includes only developers of orphan drugs, and "All Therapeutics" includes all drug developers, both categories exclusive of diagnostics and tools.
2020 Mega M&A – Dec. AstraZeneca/Alexion $39B (included in rare disease numbers)
Source: DealForma and Global Genes
Analysis: Global Genes

2022 Rare Disease Venture Financing by Indication, (USD M)

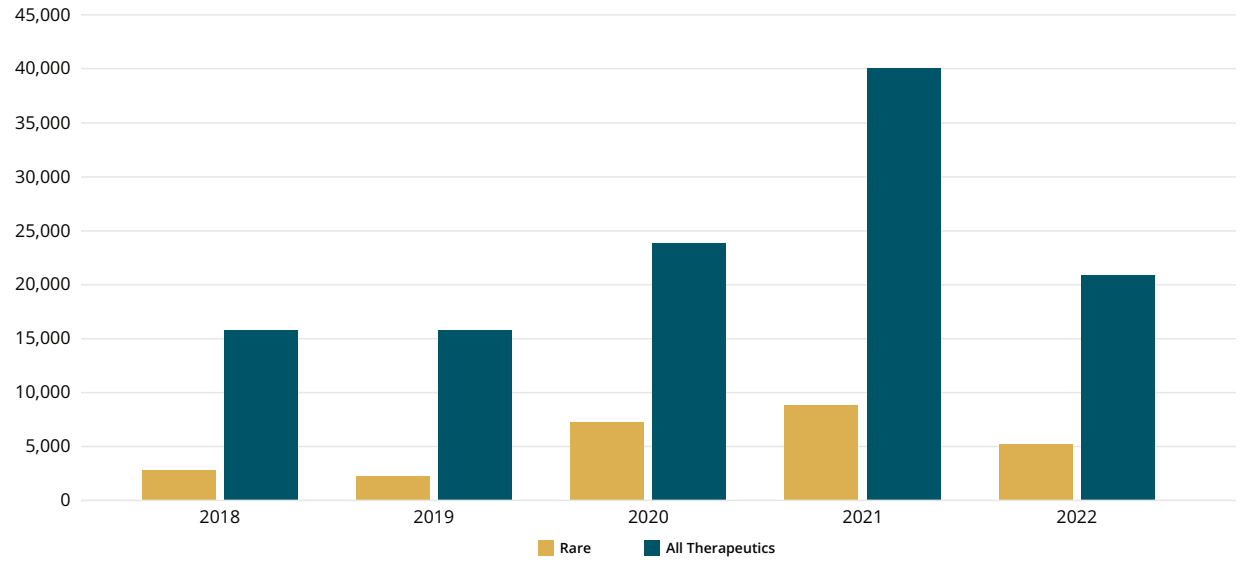


2022 Rare Disease Venture Financing by Platform Technology, (USD M)



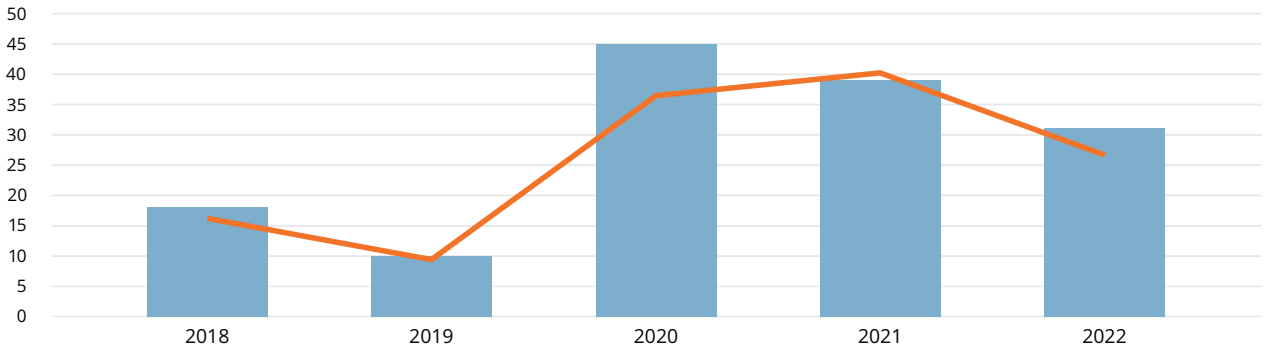
Source: DealForma and Global Genes

Venture Capital Financing for Therapeutics 2018-2022 (USD M)



Source: DealForma and Global Genes

Rare Disease Series A Venture Rounds



Source: DealForma and Global Genes

percent of the total venture capital raised by rare disease drug developers. This included a $300 million series C financing completed by Tessera Therapeutics, which is developing therapies based on its Gene Writing platform that can make permanent alterations to the human genome to address virtually any type of genetic alteration.

Tessera's said its platform technology can change any base pair to any other, make small insertions or deletions, and write entire genes into the genome with delivery of only RNA. This unlocks the potential to cure nearly any genetic disease, create therapies for other serious conditions such as cancer, and prevent illnesses.

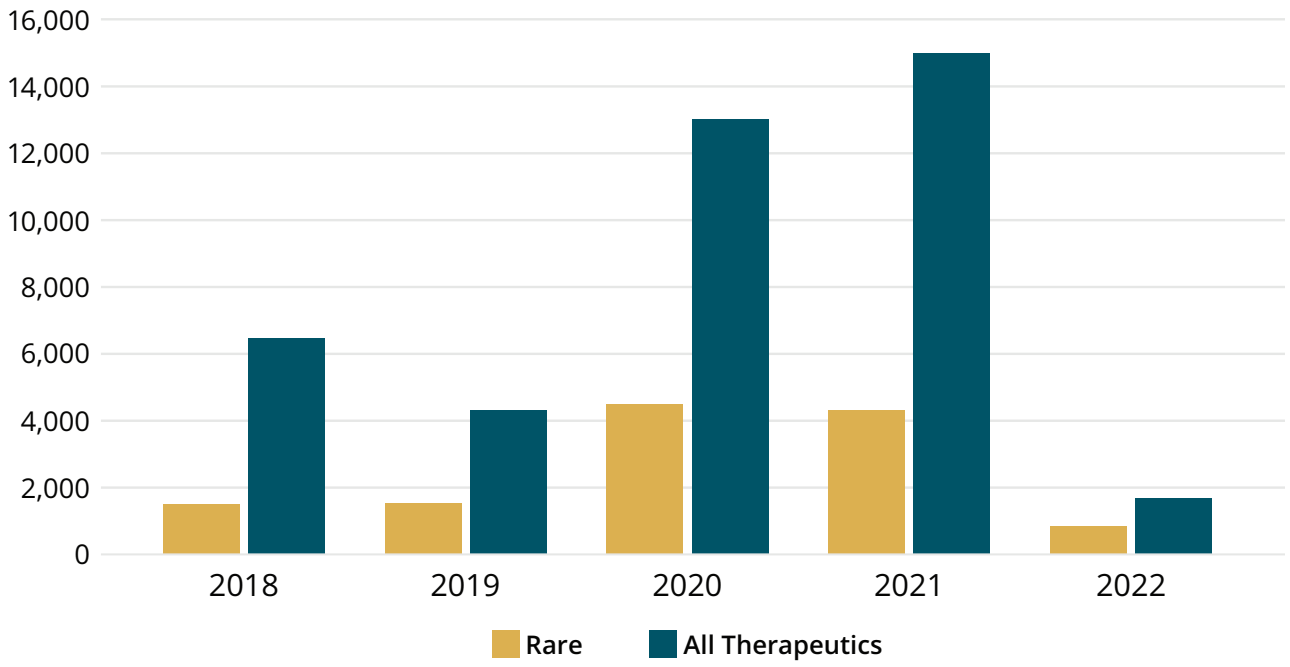
"While there have been many advancements in the area of genetic medicine over the past decade, Tessera's Gene Writing platform is charting an entirely new course—one that aims to revolutionize genetic medicine as we know it," said Noubar Afeyan, co-founder and chairman of Tessera Therapeutics and founder and CEO of Flagship Pioneering.

IPOs Slow

Though the IPO window did not close, investor appetite for rare disease therapeutic developers curbed significantly in 2022 with stocks in the sector depressed. Rare disease drug developers raised a total of $833 million through initial public offerings, down 41 percent from the total rare disease IPO funding in 2021. There was, however, a bigger percentage drop in overall drug developer IPO activity as the therapeutics sector raised $1.7 billion through initial public offerings, an 89 percent drop from the $15 billion in drug developer IPOs in 2021.

A total of six rare disease drug developers braved the IPO market with Amylyx Pharmaceuticals taking the biggest haul, raising $246.3 million, which included the exercise of its underwriters' overallotment. The company is developing therapies for neurodegenerative diseases. At the end of September, the company won approval for Relyvrio for the treatment of the neurodegenerative condition amyotrophic lateral sclerosis. Clinical data showed the drug helped slow progression of the condition. Capitalizing on the

Therapeutic Developer IPOs 2018 to 2022 (USD M)



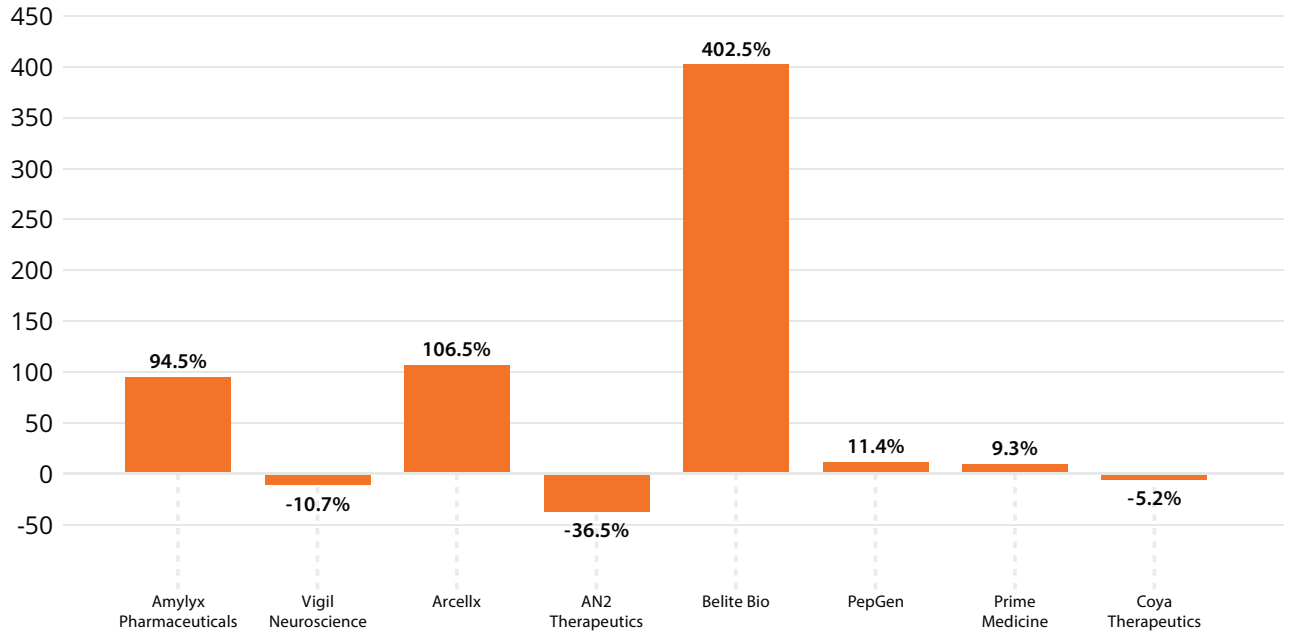
Source: DealForma and Global Genes

Rare Disease Therapeutics IPOs on U.S. Exchanges in 2022

Date Completed	Location	Company	Ticker	Total Raised ($M)	Shares Sold (M)	Price Per Share ($)	Description	Technology	Stage	First Day Price Change	Offering Price	Share Price 12/30/2022	Change since IPO
1/7/2022	U.S.	Amylyx Pharmaceuticals	AMLX	190	10	19	Neurologic (ALS)	Small molecule	Phase 3	-5%	19	36.95	94.5%
1/7/2022	U.S.	Vigil Neuroscience	VIGL	98	7	14	Neurodegenerative (antibodies)	Antibody	Phase 1	-10%	14	12.5	-10.7%
2/4/2022	U.S.	Arcellx	ACLX	142.3	9.5	15	Rare cancer	Cell therapy	Phase 1	12%	15	30.98	106.5%
3/25/2022	U.S.	AN2 Therapeutics	ANTX	69	4.6	15	Rare infectious	Small molecule	Phase 2/3 ready	3%	15	9.53	-36.5%
4/29/2022	U.S./ China	Belite Bio	BLTE	36	6	6	Retinal degeneration	Small molecule	Phase 3	77%	6	30.15	402.5%
5/6/2022	U.S.	PepGen	PEPG	108	9	12	Neuromuscular	Oligonucleotides	Phase 1	7%	12	13.37	11.4%
10/20/2022	U.S.	Prime Medicine	PRME	175	10.3	17	Genetic diseases	Gene editing	Preclinical	-10%	17	18.58	9.3%
10/29/2022	U.S.	Coya Therapeutics	COYA	15	3.1	5	Neuro/ Autoimmune	Biologics	Phase 2	-8.60%	5	4.74	-5.2%

Source: DealForma and Global Genes

Aftermarket Performance of 2022 Rare Disease Therapeutics IPOs (12/31/2022)



Source: DealForma and Global Genes

approval, Amylyx raised an additional $246 million through a secondary offering in October.

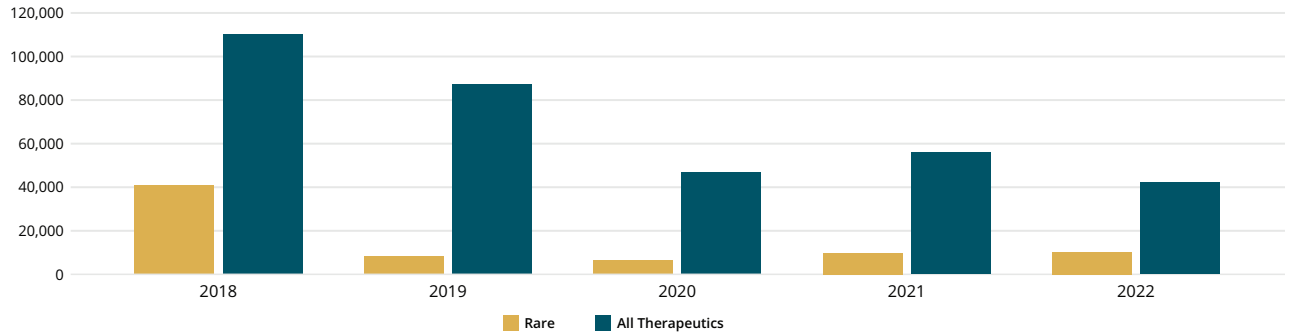
Public equity and debt offerings (excluding IPOs) for rare disease drug developers rose to $10.3 billion in 2022, up 5 percent from the previous year. Even though it was a modest increase from the $9.8 billion raised in 2022, it represented the only uptick in any category of financing in 2022 for rare disease drug developers. Overall, drug developers raised $41.7 billion through the sale of public equity and debt (excluding IPOs). That represented a 25 percent drop from 2021.

The numbers include the $410 million financing by Blueprint Medicines, which was the biggest user of debt financing among rare disease drug developers. The company raised a total $410 million through a credit facility in 2022 as it looked to strengthen its financial muscle with the global launch of two therapies: Ayvakit to treat adults with advanced systemic mastocytosis or certain types of gastrointestinal stromal tumors, and Gavreto for certain cancers caused by an abnormal RET gene.

Dealmaking Activity Down

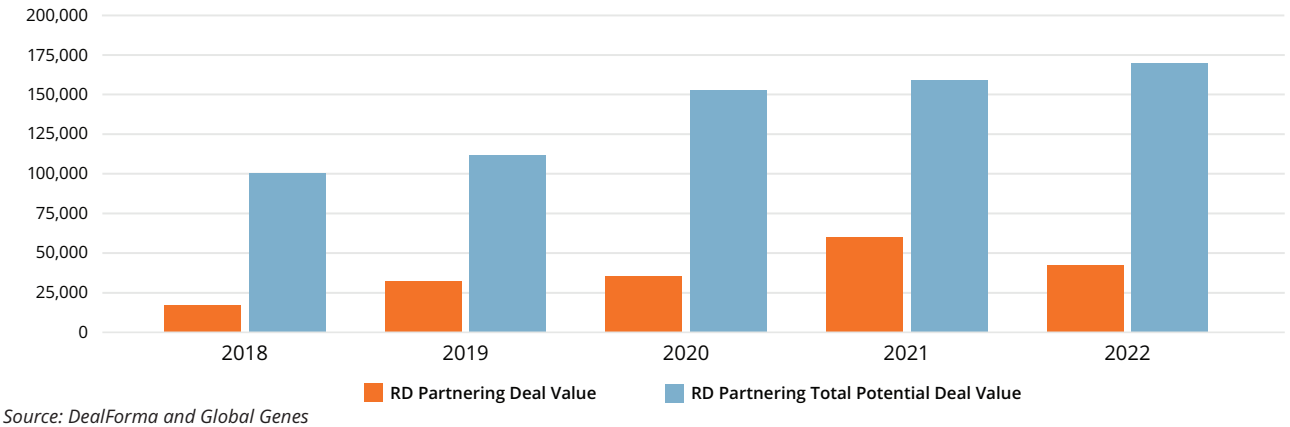
Rare disease partnering deal values at signing fell to $2.6 billion in 2022, a 45 percent decline from the same period a year ago. That compared to a 21 percent drop in the value at signing for partnering deals of all therapeutic developers during the year.

Public Therapeutics Debt and Equity Financings Excluding IPOs 2018 to 2022 (USD M)



Source: DealForma and Global Genes

Total Potential Value of Partnering Deals 2018 to 2022 (USD M)



Source: DealForma and Global Genes

Pfizer paid $300 million at close for a four-year, exclusive research collaboration with Beam Therapeutics to advance Beam's novel *in vivo* base editing programs for three targets for rare genetic diseases of the liver, muscle, and central nervous system. The deal is worth up to $1.4 billion. Beam's base editing technologies are designed to enable a new class of precision genetic medicines that target a single base in the genome without making a double-stranded break in the DNA to create a more precise and efficient edit compared to traditional gene editing methods.

Poseida Therapeutics' deal with Roche to develop off-the-shelf CAR-T therapies directed at hematologic malignancies, represented the largest potential deal value in the rare disease space in 2022 with a total potential value of up to $6.2 billion. The deal carried an upfront payment of $110 million.

The agreement provides Roche either exclusive rights or options to develop and commercialize a number of allogeneic CAR-T programs in Poseida's portfolio that are directed to hematologic malignancies, including P-BCMA-ALLO1, an allogeneic CAR-T for the treatment of multiple myeloma and for which a phase 1 study is underway, and P-CD19CD20-ALLO1, an allogeneic dual CAR-T for the treatment of B-cell malignancies with an application to begin human clinical trials expected in 2023.

A Notable Acquisition

For most of 2022, M&A activity was a bit lackluster until December when Amgen announced it would acquire Horizon Therapeutics for $28 billion. It was one of only six rare disease drug developer M&A deals with a value in excess of $1 billion in 2022. It pushed the total rare disease drug developer acquisitions to $51.8 billion, a modest 1.5 percent decline from the $52 billion in transaction values in 2021. Overall, drug developer M&A activity remained flat for 2022 as total deal values reached $103.3 billion, a 6 percent increase from the $97.8 billion in M&A value in 2021.

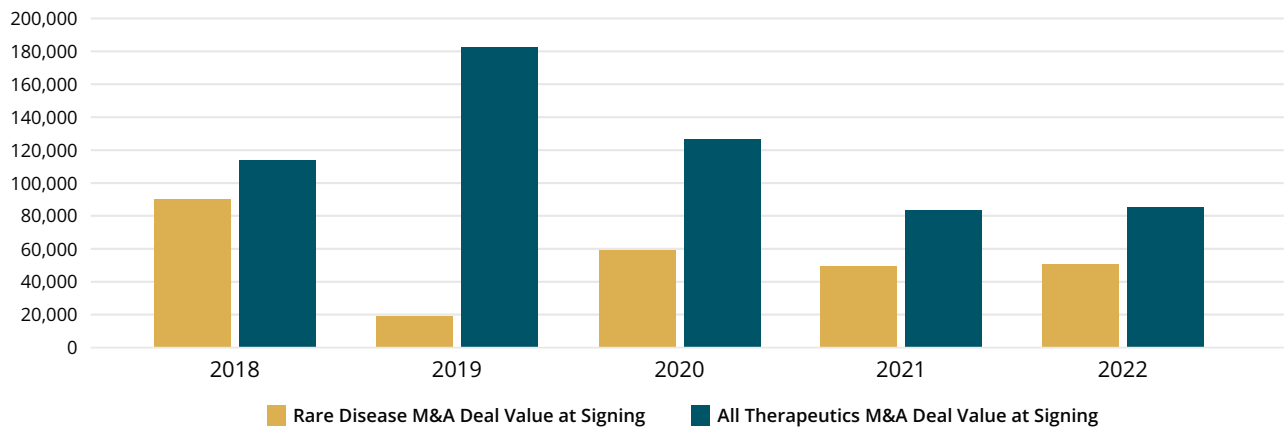
"In nearly 15 years, we have built one of the fastest growing and most respected companies in the biotechnology industry from the ground up, which are all rooted in our employees' deep commitment, dedication, and personal passion for those impacted by rare, autoimmune and severe inflammatory diseases," said Tim Walbert, chairman, president, and CEO of Horizon Therapeutics. "Amgen is aligned with that commitment and passion and will continue to maximize the value of the current portfolio and pipeline and accelerate the ability to reach more patients globally."

Horizon Therapeutics is headquartered in Dublin, Ireland with more than 2,000 employ-

"In nearly 15 years, we have built one of the fastest growing and most respected companies in the biotechnology industry from the ground up."

—Tim Walbert

Therapeutic M&A Deals at Signing (USD M) 2018-2022



Source: DealForma and Global Genes

ees and is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. The company has 12 marketed medicines, including recently approved first-in-class medicines Tepezza, Krystexxa, and Uplizna, and a pipeline with more than 20 development programs.

For Amgen, the acquisition is expected to strengthen its portfolio of first-in-class / best-in-class innovative therapeutics by adding a complementary portfolio of medicines from Horizon that address the needs of patients suffering from rare diseases and capitalizes on Amgen's legacy in inflammation and nephrology and its global scale to enhance the growth potential of Horizon's portfolio.

The sector should continue to be strengthened by advances in innovation and the growing ability of rare disease therapeutics developers to advance therapies that not only provide meaningful treatment for conditions with unmet needs, but evolving modalities that can address the underlying cause of genetic diseases and provide functional cures.

Using Cryptocurrency to Tap Into the Wisdom of Crowds

Alok Tayi spent about 15 years as a bench scientist until his wife gave birth to their daughter, who was born with an illness that required her to spend a long time in the neonatal intensive care unit. While the infant didn't suffer from a rare disease and the biology was well understood, there were no dedicated therapeutic options available to her.

Tayi ended up spending a lot of time with other families with sick children in the NICU, particularly parents of children with rare diseases.

"The one thread that tied us all together was the fact that though we all had tremendous hope that a treatment could be brought to bear to treat our child, unfortunately we all lacked the capital required to be able to bring those medicines to market," he said. "It was from that experience that I drew the insight that ultimately, in this domain of rare diseases, the challenge is not finding a potential treatment, it's actually funding it."

Tayi and co-founder Joshua Forman founded Vibe Bio after Tayi's daughter was born. Having spent a considerable amount of time in the NICU, Tayi worked to develop a different approach to developing therapeutics—one that taps new sources of capital from the cryptocurrency world and empowers the patients who would benefit most from new therapies.

Vibe Bio takes it cue from the world of cryptocurrency. It is a decentralized autonomous organization (DAO), and is building a community of patient advocates and investors where holders of a crypto currency token Vibe sells get to vote on how to invest its pool of money in rare disease drug development efforts. Once a decision is made to invest in the development of a therapy, Vibe creates a traditional corporation and uses conventional financing mechanisms.

The company says its DAO will serve as an online coordination hub for its diverse stakeholders, connecting patient communities directly to investors, scientists, and other experts. Members will have the power to vote on which rare disease research proposals to pursue, as well as nominate specific diseases or candidate medicines. The proposals will each be vetted by scientists and financial experts.

Within that structure, Tayi said patient communities are given a central role. He says the intent is to put "patients in the driver's seat of drug development."

A Mixed Outlook

Companies' ability to raise capital in 2023 will likely be closely tied to clinical results as investors' appetite for risk has dampened with biotech stocks down sharply over the past two years. While venture investors have plenty of capital to deploy, the companies that seem best able to attract money are those working on advanced therapies including genetic medicines and cell therapies.

With new gene therapies reaching the market in 2022, and more expected in 2023, investors will be closely watching to see if these promising therapies can become market successes, or whether their hefty price tags will short-circuit their success. Pricing on other innovative therapies will also be closely watched to see if the market values these new medicines as much as their developers.

Amgen's acquisition of Horizon has boosted interest in the sector. Investors have been waiting to see a pick-up in M&A activity. Should that occur, investors should find themselves once again enamored with the rare disease focused drug developers. ■

"Vibe empowers patient communities to be a key constituent within this community and can put forth proposals in terms of drug development for diseases that they care about. Patient communities can also vote and decide what the prioritization of these proposals are and fund them using capital from the DAO. Lastly, patient communities also have economic ownership of the C Corp associated with their disease," he said. "As those medicines are being developed, Vibe, at the end of the day, is providing unprecedented ownership for patients in the drug development process by giving them a say, in terms of what's pursued, on its priority."

"Ultimately, in this domain of rare disease, the challenge is not finding a potential treatment, it's actually funding it."

—Alok Tayi

Vibe has already partnered with two patient advocacy organizations to launch and fund independent biotechnology companies to pursue promising therapeutics for rare and often fatal diseases. With Chelsea's Hope, a patient advocacy organization dedicated to curing Lafora disease, a fatal form of progressive myoclonus epilepsy that presents in children and adolescents, Vibe Bio is launching New Hope Therapeutics.

It also partnered with NF2 Biosolutions, a patient advocacy organization accelerating gene therapy research for neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system, to launch Merlin Therapeutics.

The intellectual property from the ventures will be owned by the independent biotechnology companies.

In June 2022, the company announced its launch with $12 million in funding to scale the development of therapies. Though that may not represent a lot for drug development, Tayi believes the company will be able to leverage that.

"The initial capital that we've raised allows us, with fairly modest quantities of capital, to actually be able to advance these medicines into later stages of development, including clinical trials. The interesting thing about the rare disease space is that it only costs a few hundred thousand dollars, maybe even a few million dollars, to be able to advance these medicines to a point where you can get to a clinical proof-of-concept," he said. "What ends up happening is that the initial capital that we allocate allows these programs to advance, but also can attract more traditional financing or other sources of capital to support it as well."

Payers and Policymakers Eye Rare Disease Spending

"There is a need to prioritize rare diseases as a public health crisis…It doesn't have the voice that somebody with cancer or Alzheimer's has right now."

— Gina Cioffi, senior manager of public affairs for Global Rare Diseases at Chiesi Group

In the United States, the landmark Orphan Drug Act of 1983 has been under attack. Since the passage of the act, which provides financial incentives to encourage the development of drugs to treat rare conditions, there has been an acceleration of the approval of therapies for orphan indications. For the last several years, around half of all novel drugs the U.S. Food and Drug Administration approved were to treat orphan diseases. With nearly 11,000 rare diseases identified and more being discovered each year, most diseases—more than 90 percent—continue to have no approved therapy. Nevertheless, the growing number of therapies and the relatively high prices they command have payers and policymakers searching for ways to control spending on these medicines.

"This unmet need is an enduring part of the orphan disease landscape, but it is now shadowed by a problem not foreseen by the authors of the ODA," write the authors of a 2022 report on orphan drug policy considerations from the Institute for Clinical and Economic Review and researchers at NORC at the University of Chicago. "The rapid growth in approved rare disease treatments in recent years has created concerns about the pricing of orphan drugs and their cumulative affordability to the health system."[16]

At the same time, growing awareness of the financial burden on families of people with rare diseases has patient advocates not only looking to push back on efforts to pare back incentives to drug developers to pursue treatments for orphan indications, but also find new ways to ease the burden on them. Outside the United States, particularly in low- and middle-income countries, rare disease patients are left without access to needed medications as governments seek to develop policies to create mechanisms to pay for these therapies. As pressures mount, the push and pull over the direction of policy is intensifying, leaving rare disease advocates to fight battles on many fronts at once as they fear policies could have unintended consequences of discouraging biopharmaceutical companies from pursuing new treatments for rare diseases.

The ICER report, which didn't endorse any specific approaches, reviewed four broad categories of policies. They included measures to encourage ultra-rare drug development, limiting incentives for orphan drugs approved for non-orphan indications, strengthening evidence generation, and steps for reducing the price for rare disease products. The list of pricing policies considered mechanisms such as outcomes-based contracts, using indication-based pricing, pursuing value-based pricing, or volume-based contracts.

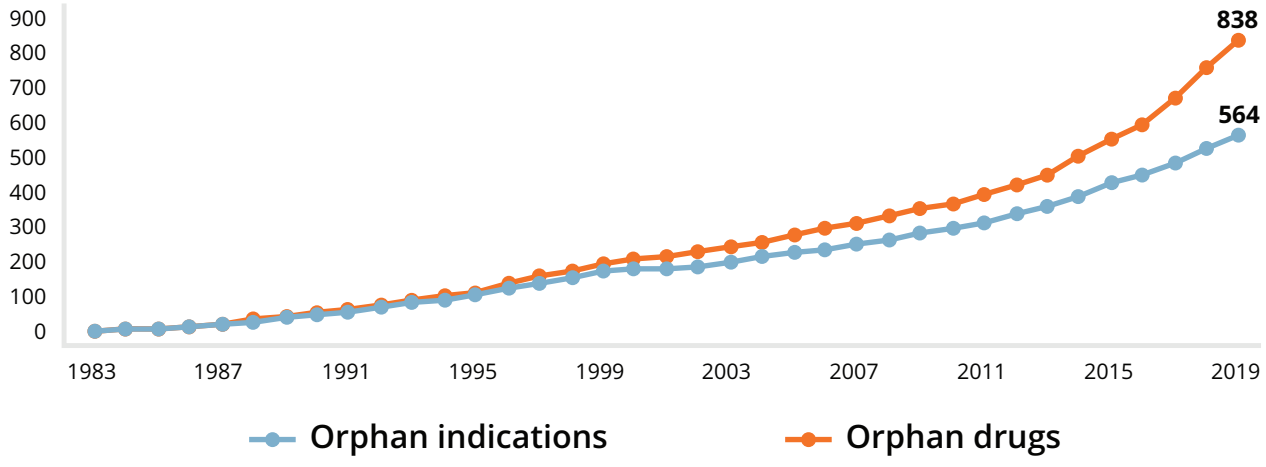
"Policymakers and stakeholders will need to consider carefully whether these policy reforms would be able to retain the special incentives needed to ensure continued investment in orphan drugs while creating a better balance between the joint goals of broad innovation and affordability," the authors of the ICER report write. "Views will differ, however, one thing is certain: continued innovation will only prove sustainable and helpful to patients if the costs of the overall effort of innovation can be better managed, both for individual patients and for health systems and society."

Rethinking Orphan Policies

In the United States, the Orphan Drug Act continues to face attacks. The act provides a tax credit for qualifying clinical trials costs, an exemption from marketing application fees, and seven years of market exclusivity for an approved indication to treat a patient population of 200,000 or fewer in the United States. The act also provides drugmakers an exemption from having to sell medicines that have an orphan drug designation at a reduced price to providers qualified under the government's 340B discount program.

In 2017, the Orphan Drug Act lost some of its punch when Congress passed the *Tax Cut and Jobs Act*, which reduced the total amount of the tax credit for qualifying clinical testing expenses to 25 percent from 50 percent. Though critics sought to impose additional restrictions in the legislation that became a precursor to the Inflation Reduction Act of 2022—an elimination of the tax credit for all but the first approved orphan uses of a drug—those efforts failed to be included in the final form of the legislation that passed.

Cumulative Number of Approved Orphan Indications and Distinct Drugs With at Least One Orphan Indication by Year of Marketing Approval



Source: The Next Generation of Rare Disease Drug Policy: Ensuring Both Innovation and Affordability; Institute for Clinical and Economic Review

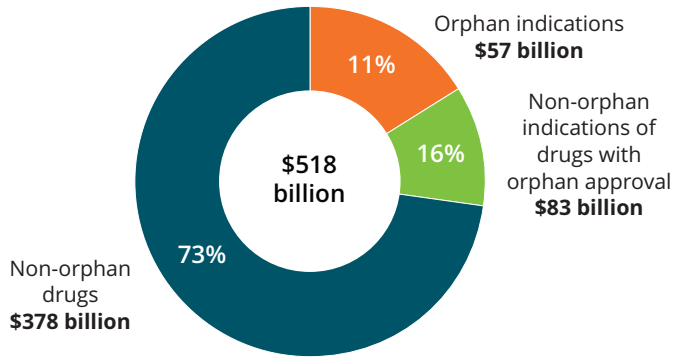
Critics of the Orphan Drug Act say it was intended to incentivize the development of drugs for small patient populations, but drugmakers are often successful at expanding the indications for orphan drugs to include large market opportunities that turn them into multi-billion blockbusters without losing any of the benefits conferred on them from the act. A September 2021 report from the Office of Inspector General of the U.S. Department of Health and Human Services examined what is called a "purposeful" sample of 40 high-expenditure drugs in Medicare and found that some of the world's best-selling drugs had an orphan drug designation for at least one indication. The orphan status has been used to justify the high price of a drug, but once expanded to more common indications, drugmakers do not alter their pricing.

The report found that 22 of the 40 high-expenditure Medicare Part B and Part D drugs included in the Office of Inspector General Report had approvals for at least one orphan indication. While the report noted that less than 20 percent of all orphan drugs are approved to treat common diseases or conditions in addition to their orphan-designated rare diseases, 15 of the 22 orphan drugs examined in the report also had approvals for common diseases or conditions. Of the 22 orphan drugs on the list, 19 had U.S. sales in 2018 of $1 billion or more. One drug—the TNF inhibitor Humira—had global sales approaching $20 billion. That's led to a repeated refrain among industry critics that drug companies have exploited the Orphan Drug Act to game the system.

In Europe, efforts to reform the Orphan Medicinal Products Regulation are underway. Policymakers are seeking to address shortcomings in the existing framework with the goal of sharpening the focus on areas of high unmet needs for patients. They are also seeking to simplify and streamline the evaluation of medicines for rare diseases to reduce the burden on companies and regulators. Changes to the regulation are expected to be released before the end of 2023.

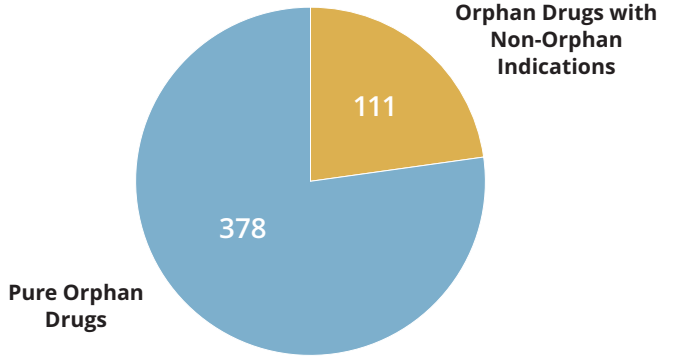
In June 2022, the European Federation of Pharmaceutical Industries and Associations and the rare disease organization Eurordis, despite areas of disagreement, issued a joint statement on revisions to the Orphan Medicinal Products Regulation with proposals to ensure broader and faster access to needed medicines for patients in Europe. It is the first time the two organizations have collaborated on a joint statement of any kind. Though the regulation is widely viewed as a success to bringing innovative medicines to the as many as 36 million people in Europe living with a rare condition, access to therapies have been uneven. Only 37 percent of orphan products are available across Europe and access varies from country to country with nearly none of them available in Lithuania and nearly all of them available in Germany.

Invoice Spending on Orphan Drugs in the United States 1992-2012 (USD Billions)



Source: The Next Generation of Rare Disease Drug Policy: Ensuring Both Innovation and Affordability; Institute for Clinical and Economic Review

Approved Orphan Drugs Through 2017



Source: The Next Generation of Rare Disease Drug Policy: Ensuring Both Innovation and Affordability; Institute for Clinical and Economic Review

In addition, the two organizations report the lack of access is compounded by an estimated average delay of 636 days between when an orphan product wins marketing authorization and when patients can access them.[17]

The two organizations put forward three sets of proposals to address the complex issues that impair access to medicines for patients with rare diseases in Europe. The proposals seek to address equity of access, pricing and reimbursement, and the stimulation of translational research.

"Often European and national policies cannot progress because the analysis of the issues is unclear, the solutions are not identified, or there is no consensus among the stakeholders," said Yann Le Cam, CEO of Eurordis-Rare Diseases Europe. "Here, in rare disease therapies, there is a wide agreement on the issues of access and their root causes, there are concrete solutions designed over the years through robust work embedded in real-life experience and multi-stakeholder dialogues, and now there are clear common positions amongst stakeholders."

Rethinking Pricing and Payment

Among the proposals put forth in the EFPIA-Eurordis statement is one that lays out a conceptual framework for international differential pricing, or what they call "equity-based tiered pricing." The idea of such an approach is to improve access and affordability in lower-income EU countries without discouraging companies from making investments in the development of innovative therapies.

Under the proposed framework outlined by the two organizations, lower prices would be available to less wealthy EU member states. Steps would need to be taken to ensure medicines sold under the framework in less wealthy states would not be diverted to wealthier markets. The plan calls for that agreement to be paired with a commitment from member states to complete pricing and reimbursement decisions within 180 days. The two organizations, while they agree on the principle of equity-based tiered pricing, differ on how to set prices. The EFPIA said the equity-based tiered pricing should not be viewed as an alternative to value-based pricing but built on a foundation of it. Eurordis, though, calls for a cross-country collaboration to establish a single EU price anchor for each product.

The drug giant Pfizer, shortly after the release of the joint EFPIA-Eurordis statement, argued among the innovations that will be necessary to allow rare disease patients to benefit from emerging, one-time gene therapies will be new approaches to payment structures. "The potential one-time approach of gene therapy requires a change in the way we think about affordability and may necessitate shifting away from the traditional 'pay-per-prescription' template," the company wrote in an opinion piece published on the website of *The Parliament Magazine*. "Novel reimbursement approaches for gene therapy include pay-for-performance (response to treatment), value-based agreements, and pay-over-time financial models. The goal is to allow payers to manage clinical uncertainty, budget impact, and sustainability of the healthcare system, while providing recognition of the potential long-term value and innovation being delivered for many rare diseases."[18]

Such an approach could increase access and affordability, as well as allay payers' concerns about the use of costly new therapies in the absence of clear evidence of their value. While this is a concern that weighs on one-time, potentially curative therapies where the long-term durability of the treatments remains unproven, it also extends to high-priced therapies where payers may be slow to accept existing evidence of medicines' efficacy to support their value, or patients may balk at the large co-payments they must make for these therapies. To address these concerns, drugmakers have begun to roll-out novel pricing mechanisms.

When Bluebird Bio won approval in August 2022 for Zynteglo, its gene therapy for beta thalassemia, it unveiled a pricing strategy intended to provide flexibility to payers and address their needs. Under the plan, the company will charge an upfront payment that can be paired with an outcomes-based agreement. Bluebird said it will reimburse contracted commercial and

"Often European and national policies cannot progress because the analysis of the issues is unclear, the solutions are not identified, or there is no consensus among the stakeholders."

— Yann Le Cam

An Effort to Soften Co-Payments Runs Into a Legal Obstacle

The large co-payments that rare disease patients can face could pose a barrier to treatment or take a toll on patients' personal finances, even when they have insurance coverage.

Pfizer sought to soften that blow for people with the rare and progressive heart condition transthyretin amyloid cardiomyopathy (ATTR-CM) by directly covering the $13,000 copayment for its medicine Vyndaqel while making patients responsible for just $35 a month.

A United States Court of Appeals for the Second Circuit upheld a lower court ruling that Pfizer's co-payment for Vyndaqel violated a federal anti-kickback statute.

A three-judge panel sided with the U.S. Department of Health and Human Service Office of Inspector General, which had issued an advisory opinion in 2019 that found Pfizer's Direct Copay Assistance Program for Vyndaqel violated the law. A district court in September 2021 granted a summary judgement to HHS when Pfizer first brought suit as it rejected the drugmaker's argument that the anti-kickback statute requires an element of "corrupt" intent.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by destabilization of a transport protein called transthyretin, which is composed of four identical subunits known as tetramers. In ATTR-CM, heart failure occurs when unstable tetramers dissociate, resulting in misfolded proteins that aggregate into amyloid fibrils and deposit in the heart.

Vyndaqel is a small molecule drug that selectively binds at specific sites on the transthyretin tetramer to prevent destabilization of the transthyretin transport protein and formation of amyloid that causes ATTR-CM. Vyndaqel is the only drug approved by the U.S. Food and Drug Administration to treat ATTR-CM. It's an expensive drug with an annual cost of $225,000 per year.

The anti-kickback statute was established to combat Medicare and Medicaid fraud. It prohibits providing any payment to induce a person to buy a federally reimbursable healthcare product. The court rejected the company's argument that there must be a corrupt intent and found that both the court and HHS had properly interpreted the plain meaning of the statute.

government payers up to 80 percent of the cost of the therapy if a patient fails to achieve and maintain transfusion independence up to two years following infusion. The company said the outcomes measure is recognized by payers and providers as clinically meaningful and straightforward to track through claims data.

When the nonprofit drug value watchdog ICER in a draft evidence report calculated the lifetime cost of managing hemophilia A among clinically eligible patients using one-time administration with BioMarin's Roctavian compared to the bispecific antibody emicizumab, which is used to reduce and prevent bleeding episodes, ICER used treatment, treatment-related adverse events, treatment for bleeding episodes, arthropathy, surgery, and non-drug costs in creating its model. The organization assumed an annual cost of hemophilia therapy emicizumab of $640,000 per year and the one-time Roctavian price to be $2.5 million. ICER modeled the effect of Roctavian to last 12 years (before patients were assumed to switch back to prophylaxis) for the entire cohort post infusion.

ICER calculated a greater than $4 million cost saving per patient over a lifetime with projected improvement in quality of life. The organization, in making its calculations, incorporated an outcomes-based warranty agreement in its base-case economic model, something BioMarin said it plans to offer that will provide risk-sharing for a period of four years. The company said it would have it ready to implement with payers at launch. BioMarin's application in the United States has been submitted to the FDA and is expected to be acted on in 2023. At press time, the company had not provided details on its pricing or warranty program.

Other makers of high-priced rare disease therapies are taking steps to reduce financial risks to patients. Consider Pfizer, which won approval for Panzyga, its treatment for the rare neurological disease of the peripheral nerves, chronic inflammatory demyelinating polyneuropathy (CIDP). Pfizer in August 2022 unveiled a warranty program for the drug. The company said it will refund the out-of-pocket amount that patients who meet the eligibility requirements paid for up to the first four treatments of Panzyga for CIDP, up to a maximum of $16,500 per treatment. Pfizer said it would refund no more than a total of $50,000. There are certain restrictions to the program relating to whether the drug was covered in whole or in part by

certain state and federal programs. Patients seeking to take advantage of the warranty program must discontinue use of Panzyga prior to taking the fifth dose. The drug must have been used to treat CIDP, prescribed by the patient's healthcare provider, and stopped at the discretion of the healthcare provider.

The pricing and risk-sharing challenges drug companies face are complicated by country-to-country differences with regard to payment systems, measures of value used, and who is making the determination of value. The simple fact that the direct beneficiaries of a therapy in most cases are not the ones paying for it also adds to a potential conflict between the payer and the patient.

While many countries are grappling with how to pay for rare disease therapies, the efforts vary and often depend on how advanced the economy of a particular country is, whether it is a single-payer healthcare system, and how established its overall approach to rare diseases may be, if it exists at all.

Paying for Innovation

In England, the National Health Service said patients will get early access to potentially life-saving and cutting-edge treatments thanks to up to $427 million (£340 million) that has been made available through the Innovative Medicines Fund to purchase the most promising medicines and fast-track them to patients. Rather than making patients wait until cost-effectiveness data is available, this new plan will provide access to certain new medicines with support from NHS England and the National Institute for Health and Care Excellence (NICE).

The fund will further support NHS England in offering patients potentially transformative new drugs while collecting real-world evidence to inform a final decision by NICE, its watchdog on the value of medicines, in determining whether a treatment is clinically effective, cost effective, and a good use of taxpayer money. The plan is intended to reduce delays and boost patient outcomes in the interim.

Already similar efforts have been made to enable patients to access certain rare disease therapies. "This new Innovative Medicines Fund will build on the success of the Cancer Drugs Fund, enabling more patients to benefit from early access to the most promising cancer and non-cancer medicines," said Blake Dark, commercial medicines director at NHS. In the past five years, the Cancer Drugs Fund has provided more than 80,000 people access to life-extending or potentially life-saving drugs which might otherwise not have been available for years. A total of $738 million (£680 million) has been set aside for the Innovative Medicines Fund and Cancer Drugs Fund—$369 million (£340 million) each—to fast-track medicines to NHS patients. All medicines deployed through the Innovative Medicines Fund and Cancer Drugs Fund must be approved by the Medicines and Healthcare products Regulatory Agency (MHRA) after meeting standards of safety and quality and must be recommended as suitable for the fund by NICE.

In South Korea, the issue of access drew some attention when Lee Jae-myung, the unsuccessful 2022 Democratic Party of Korea presidential nominee, made a campaign promise to extend national health insurance coverage to include hair loss treatments, *The Korea Times* reported. That caused outrage in the rare disease community because there is little public health insurance coverage for rare disease therapies. In Korea, a rare disease is a condition that affects 20,000 people or fewer in the country and there are an estimated 800,000 people there living with a rare disease. Korea's public health insurance coverage for orphan drugs is $311 million, just more than 2 percent of total spending on drugs.

"There are still many patients with rare life-threatening diseases, including babies born with rare disorders in this era of ultra-low fertility, and they are not guaranteed access to treatment due to the high cost of new, orphan drugs," The Korean Organization for Rare Disease said in a statement. "It is not proper to discuss expanding the coverage of national health insurance to hair loss treatment in this situation."[19]

In Malaysia, the government is establishing a trust fund and database for rare diseases by the end of 2023 to improve care as part of the Ministry

"This new Innovative Medicines Fund will build on the success of the Cancer Drugs Fund, enabling more patients to benefit from early access to the most promising cancer and non-cancer medicines."

— Blake Dark

of Health's Rare Disease Programme Strategic Plan. The Rare Disease Trust Fund will be created in partnership with rare disease patient advocacy organizations and is intended to provide sustainable funding for treatment of rare disease in Malaysia. The ministry has identified 500 rare diseases that have been found in the country.[20]

And in India, where the Ministry of Health and Family Welfare estimates between 72 million and 96 million people have a rare disease,[21] the government unveiled a crowdfunding platform to raise money from corporate and individual donors to pay for the treatment of people with rare diseases through a number of designated centers of excellence as part of its National Policy for Rare Diseases, 2021. As of the end of May 2022, 280 patients had registered for treatment under the policy.

"Insurance companies tend to have a lot more money than patients and families. They can differentiate and diversify the risk of the rare diseases."

— Giacomo Chiesi

The crowdfunding site has fallen far short of expectations raising just $14,522 (₹118,000) as of March 2022, according to a report from the Organization for Rare Diseases India.[22] The anemic fundraising has left the center of excellence unable to begin treating rare disease patients who registered with their sites. Patient advocates have suggested that the fact that contributions made to the fund are not tax deductible has been a barrier to attracting donations.[23] There are about a dozen therapies approved in India to treat rare diseases. Treatments include expensive enzyme replacement therapies to treat a number of different lysosomal storage disorders.[24]

Separately, the Indian government increased the support offered to people with rare disease by expanding a one-time grant for all rare disease patients. The government raised the amount to $615 (₹50,000) from $246 (₹20,000) for any category of rare disease patient at specified centers of excellence. Though India is a global drug manufacturing powerhouse, most people in the country are unable to afford therapies for rare diseases and none of them are manufactured in India. India's Department of Science and Technology is pursuing a strategy to get manufacturers in India to produce off-patent medicines for rare disease, as well as develop a process to make medicines available at affordable prices once their patents expire.[25]

A Public Health Crisis

In 2021, the EveryLife Foundation for Rare Diseases issued a study on the economic burden of rare disease that found the direct and indirect cost of these conditions in the United States totaled nearly $1 trillion a year. Now, a separate, 2022 study from Chiesi Global Rare Diseases, a business unit of the international pharmaceutical and healthcare focused Chiesi Group, with support from the health information technology company IQVIA, suggests that the costs could be as high at $8.6 trillion.

The Chiesi study found that the per patient, per year costs of rare diseases are more than 10 times higher than for more common diseases. The study found that the direct, indirect, and mortality costs associated with rare diseases are all higher in cases where a patient is without a treatment than in cases where a treatment exists.

"These results highlight the need for policymakers to nurture and sustain innovation based on the positive economic return from rare disease therapies and justify an increased governmental investment in diagnosis and newborn screening to ensure wider patient access to therapies," the authors wrote. "Incentives for drug development, particularly restoring the Orphan Drug Tax Credit to 50 percent and maintaining its current applicability to multi-indications, encourage investment and have led to progress in rare disease drug approvals."

The Chiesi study differed in a number of ways from the EveryLife study, but most notably in its inclusion of mortality costs—the value of lost years of life—in its calculations. It used the U.S. Department of Transportation's value of a year of life at $130,000 and a life expectancy of 79 years to determine mortality costs.

For its analysis, the Chiesi study began with a database of 373 rare diseases covering 8.4 million patients in the United States. Through consultations with rare disease experts and patient advocates, it selected 24 diseases across a range of therapeutic areas and evaluated costs in three categories: direct costs (medication,

hospitalization, home healthcare, and more), indirect costs (productivity cost for patient and caregiver, work loss, home changes, and more), and mortality costs. The availability of detailed data was also a factor in the selection of diseases for the study.

The study found for the 8.4 million patients affected with the 373 rare diseases used in the analysis, the cost is an estimated $2.2 trillion. Extrapolating its findings to include all rare disease patients in the United States, the cost is estimated to be between $7.2 trillion and $8.6 trillion.

It also found that a lack of treatment was associated with a 21.2 percent increase in total costs per patient per year, although that varied widely by indication with just a 2.2 percent increase for congenital diseases and a 51.8 percent increase for metabolic diseases.

Overall, direct cost for a rare disease without treatment totaled $118,000 per patient per year compared to $63,000 for conditions with a treatment. Indirect costs totaled $73,000 for rare diseases without a treatment per patient per year compared to $40,000 for diseases with treatment. And mortality costs totaled

A Call for the Creation of Centers of Excellence for Rare Disease in Canada

The Canadian Organization of Rare Disorders called for the development of pan-Canadian centers of excellence for rare diseases as "low-hanging fruit" that can create "immediate and significant added value to treating patients with rare disorders."

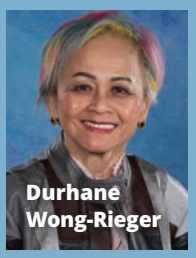
CORD made the call in an open letter to premiers about the development for a Canadian approach to improving the lives of 3.2 million Canadians living with a rare disease.

The letter from Durhane Wong-Rieger, president and CEO of CORD, noted it takes five to 10 years to get an accurate diagnosis and years more to get to the right specialist, with multiple misdiagnoses and sometimes the wrong treatment along the way. She said while it may appear to be costly to diagnose and treat, the costs of not getting a timely diagnosis and not getting access to the best treatment are much higher.

In 2015, CORD released Canada's Rare Disease Strategy, which proposed a five-point plan to address unnecessary delays in testing, wrong diagnoses, and missed opportunities to treat. In 2019, the federal government committed to improving access to rare disease therapies by investing $1 billion (CAD 747.1 million) over two years (2022-2023) to implement a national Rare Disease Drug Strategy with on-going investment of $500 million (CAD 373.6 million) annually.

In 2022, Health Canada released its proposed framework, which includes proposed investments in a number of key areas.

"We now have a once-in-a-lifetime opportunity to build on this growing momentum to implement a coordinated pan-Canadian strategy, so that every Canadian, no matter where they live, can live his/her best life," wrote Wong-Rieger. She said it's time for provincial and territorial governments to step up and add their perspectives and contributions to the proposed framework to bring into reality a Canadian Rare Disease infrastructure.


Durhane Wong-Rieger

She said centers of excellence would bring together teams of clinical experts in a nationwide network of cutting-edge facilities, with the goal to provide standards of specialized care and disease management for people living with rare disease and their families, regardless of where they live or their drug plan provider.

"Similar to how provincial cancer agencies manage all aspects of cancer in Canada, centers of excellence would present the opportunity for patients with a particular rare disease to receive the full spectrum of care and treatment for their disease," she said. "Importantly, this is also the cornerstone for how rare diseases are treated in other key jurisdictions, including the whole of Europe."

She noted that significant investments would be needed to help establish and support these centers and asked the premiers to commit dedicated funds to support the establishment of networks of centers of excellence across Canada.

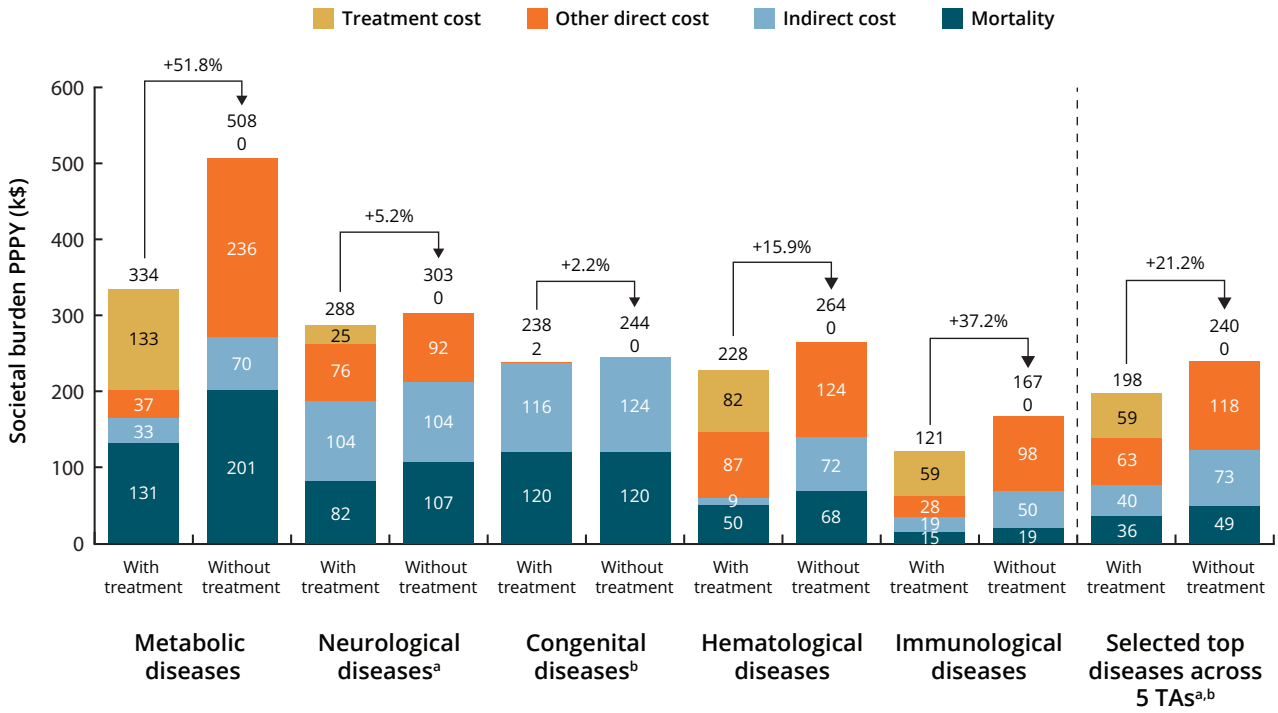
$49,000 per patient per year for rare diseases without a treatment compared to $36,000 for rare diseases with treatments.

"There is a need to prioritize rare diseases as a public health crisis. We all look at this as a societal issue. There's this notion of just science. What does data bring? What sense of justice does it bring?" said Gina Cioffi, senior manager of public affairs for Global Rare Diseases at Chiesi Group and a study co-author. "I think that here it shows that there is a really high burden, it's higher perhaps than common diseases and it doesn't get the attention, it doesn't have the voice that somebody with cancer or Alzheimer's has right now."

Giacomo Chiesi, head of Chiesi Global Rare Diseases and a co-author of the study, said much of the economic burden is left for patients and their families to contend with. He noted that while the study showed that the development of therapies reduces the burden of rare diseases overall, it also has the additional benefit of shifting part of the financial burden off patients and their families and onto payers.

"Insurance companies tend to have a lot more money than patients and families. They can differentiate and diversify the risk of the rare diseases. They can differentiate them over a portfolio of a large number of patients," he said. "Statistically, they reduce their own risks while at the same time they can finance themselves with the premiums of healthy individuals. That's a very effective way of diversifying away the financial risk of rare diseases from one single family onto society at large." ■

Burden of Disease per Patient per Year Across Rare Diseases With and Without Treatment and Value Assessment



Bars show the average burden PPPY (broken down by cost driver) associated with TAs as well as the average of selected diseases across the TAs.

[a]Excludes spinal muscular atrophy because it was an outlier in this space.

[b]From the selected top disease in congenital TA; Christianson and Deletion 5P were excluded because no treatment exists for these diseases; hence, no difference in cost magnitude.

Source: Andreu, Pedro; The Burden of Rare Diseases: An Economic Evaluation; Chiesi Global Rare Disease, 2022; https://chiesirarediseases.com/assets/pdf/chiesiglobalrarediseases.whitepaper-feb.-2022_production-proof.pdf

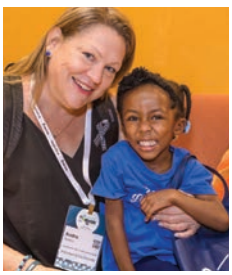
The Fierce Urgency of Now

"I am not for myself, who will be for me? If I am only for myself, what am I? And if not now, when?"

— Hillel the Elder

Patience is not always a virtue. In the world of rare disease, drug developers and patient advocates alike have come to understand that time is more valuable than money. Through ingenuity, determination, and a little luck, additional funding always seems to remain possible, but the incessant advance of time is an ever-present threat for someone seeking treatments for a progressive illness. Unlike the steady pace of the clock, the progress toward treatments and cures can face unpredictable hurdles and move in fits and starts.

Global Genes, the publisher of this report, announced in October 2022 that it would merge with the rare disease patient data sharing platform RARE-X to provide next-generation rare disease advocates the tools and resources they need to accelerate their drive to treatments. RARE-X, borne out of a need Global Genes identified in 2019, is a data sharing platform that enables rare disease patients to collect and share information that is critical to improve an understanding of rare diseases, improve the ability to diagnosis them, and accelerate the development of therapies to treat them. It is a recognition of the essential role patient data plays in changing the destiny of people with rare diseases and the need to ensure that patients control their data. It can minimize the duplication of efforts and see to it that researchers working to advance treatments have access to the data they need.



Technology continues to transform rare disease patient advocacy and give rise to next-generation patient advocates. In grammatical terms, these advocates have moved from direct objects to subjects. They are the ones taking action rather than being passive participants in their own healthcare. They are connecting to other patients from around the globe, building communities and collaborations, and conducting their own research from within their own homes.

Though there was a time when all a next-generation advocate who wanted to take a hands-on approach to drug development could do was launch their own drug company—the John Crowleys of the world—the disaggregation of research, discovery, drug development, and manufacturing has unshackled these processes from the pharmaceutical industry and given rare disease advocates the ability to access the expertise and tools along the full continuum from the lab to the patient. And the emergence of powerful information technology tools, cloud computing, and artificial intelligence are allowing individuals with modest budgets to access state-of-the-art technology that can perform sophisticated analysis that ten years ago would have required significant budgets, manpower, and time to conduct. This is enabling the creation of natural history studies, identifying approved drugs that might be repurposed to treat a rare disease, and the identification of new biomarkers, targets, and therapies.

The Ever-Changing Notion of What is Possible

Since its inception four years ago, the NEXT report has featured many next-generation patient advocates. They are redefining an ever-changing notion of what is possible for the rare disease patient community. We looked back across all four reports to pull lessons from next-generation advocates and see how they are changing the landscape.

Find a Mentor

There are many learnings to take from advocates who have come before. Next-generation advocates don't want to waste time. A perfect starting point for them is to reach out to experienced rare disease advocates who understand what it's like to face a diagnosis for themselves or a loved one for a disease without a name, an organization, or a treatment. There's no need to reinvent what already works. Starting by finding a mentor who will guide you is the fastest path to progress. It's important to learn not just what to do from your mentors but benefit from their mistakes so you can avoid making them yourself.

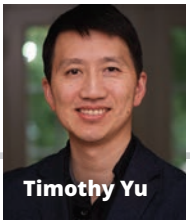
Build a Community

When Matt and Christina Might's diagnostic odyssey for their son Bertrand ended, the physicians identified him as the first person diagnosed with NGLY1 deficiency, an ultra-rare neurodevelopmental condition caused by a mutation to the NGLY1 gene. The doctors told the Mights it could be 10 or 20 years before they found another patient with the same mutation. The diagnosis could not be confirmed without finding another person with the same mutation. Matt Might realized if there was to be any chance of getting researchers to study the condition and finding possible treatments, locating other patients and their families would be essential. He wrote a blog post on his own website about the diagnosis. It was meant to serve as a beacon for any parent who was given a similar diagnosis for a child and entered "NGLY1" into a Google search. The post went viral. Within two weeks, the Mights 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 with dozens of patients identified. That was the start of building a community that has since fostered the creation of a natural history study and laid the foundation for research and work that now involves the participation of drug development companies.


Matt Might

Engage a Scientist With Vision

Julia Vitarello, whose daughter Mila was diagnosed with the CLN7 form of the deadly, neurodegenerative condition Batten disease, found the Boston Children's Hospital researcher Timothy Yu, who managed to develop a customized antisense oligonucleotide to treat her daughter in about a year's time. Though Mila has since died, the treatment provided benefits to Mila and the work has inspired countless others who recognized the potential for treating individuals or ultra-rare populations of patients with customized or so-called N-of-1 therapies. Vitarello and Yu have since launched the N=1 Collaborative to bring together academic researchers and address barriers in scaling the process. For every Julia Vitarello, there is a Timothy Yu, a visionary scientist who is willing to embrace challenges, share a patient advocate's sense of urgency, and reimagine notions of what is possible.


Timothy Yu


Julia Vitarello


Terry Jo Bichell

Leverage Commonalities With Related Conditions

Because the overwhelming majority of rare diseases are genetic, there can be a tendency to look narrowly at only people with the same genotype. In reality, despite different underlying genetic causes, many rare diseases share common phenotypes. Given the small population for many rare conditions, there's increasing recognition of how similar diseases with different genotypes can help elucidate each other and advance research into their own condition. RARE-X is pursuing this approach through the creation of consortia around disease manifestations such as vision loss, hearing loss, and sleep disruption. Terry Jo Bichell, mother of a child with the rare neurodevelopmental condition Angelman syndrome, had been a licensed nurse and board certified midwife. After her child was diagnosed, she returned to school to get a doctorate in neuroscience at Vanderbilt University. In 2020, she launched COMBINEDBrain (Consortium for Outcome Measures and Biomarkers for Neurodevelopmental Disorders). Inspired by the Angelman Syndrome Foundation's Angelman Biomarkers and Outcome Measures Alliance she once lead, COMBINEDBrain is looking across a number of genetic, non-verbal, and neurodevelopmental disorders to pool efforts on conducting studies and gathering data. These conditions need to address common obstacles, such as creating natural history studies and developing animal models, and may need to identify biomarkers and outcome measures for use in clinical trials. The hope is by collaborating, and sharing resources, tools, and experts, participating organizations can de-risk therapeutic development by working together with disorders with similar symptoms.

De-risk Research in Your Disease

The best way to attract the interest of a pharmaceutical company to pursue therapeutic development to address your rare disease is to find ways to de-risk drug development. Though the ideal way of doing this is to work with a researcher to discover and advance a therapy through preclinical development, one of the most critical things to do is to build a patient registry and conduct a natural history study. It is essential to do this work with high-grade data that regulators will accept so both drug developers and regulators can gain an understanding of how a disease manifests itself and progresses and what meaningful and measurable endpoints in a clinical study would be. Data, as has often been said, is currency.

Currency is Currency

Data may be the new currency, but money still works well. The competition for federal research grants has been well documented. The mean age of the principal investigator getting their first National Institutes of Health Research Project Grant rose to 44 in 2020.[26] While NIH has sought to address this through the introduction of grants that target the next generation of researchers, the difficulty many talented researchers face is an opportunity to fund and engage innovative scientists. The challenge most rare disease advocates face though, is not spending money, but raising it. Though successes like the ALS Ice Bucket Challenge, which raised $115 million, enter the popular imagination, fundraising is hard work that requires relentless efforts. While there are some rare disease advocates who have the personal wealth to fund research efforts, most have to hustle to raise money. Successful advocates overcome any shyness they may have about making an ask. But to fund therapeutic development, organizations like CureDuchenne and the Foundation for Fighting Blindness have followed the lead of the Cystic Fibrosis Foundation and created venture philanthropy funds. These funds allow for a focused pursuit of therapeutic development while attracting capital alongside them and providing for the potential of returns that can be used to pursue additional therapies. In 2014, the Cystic Fibrosis Foundation sold royalty rights to treatments developed by Vertex Pharmaceuticals for $3.3 billion.[27]

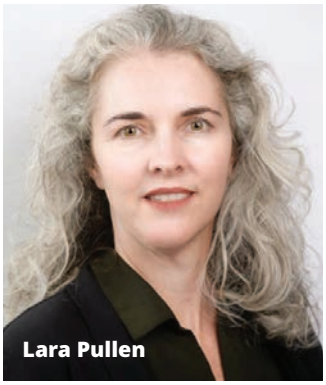
Become the Expert of Your Disease

Though people are often deferential to physicians, rare disease patients and their families often have greater knowledge and understanding of a rare disease than the doctors who may treat them. Next-generation patient advocates need to respect their own knowledge and help educate physicians about their disease. Consider Sandra Bedrosian-Sermone, whose son Tony was one of the first people in the world to be diagnosed with the ultra-rare neurodevelopment disorder ADNP syndrome. Despite being a stay at home mom whose formal education culminated in a GED credential, Bedrosian-Sermone created a parent-generated patient registry that led to her collaboration with researchers. She identified the first biomarker for the condition, co-authored five papers in peer-reviewed scientific journals, and has been sought out by scientific journals to review others' papers on the condition. She's even filed for a patent for the use of ketamine as a potential treatment for ADNP syndrome. Through her research with another ADNP parent, she made the case for repurposing ketamine for ADNP and convinced researchers at the Seaver Autism Center at Mount Sinai of the scientific merit for doing so, and they launched a clinical trial to test the theory. Despite the lack of formal scientific training, next-generation advocates frequently engage with scientists, read journal articles, and compare notes and observations with other patients and parents to make themselves experts in their disease.

Sandra Bedrosian-Sermone and son Tony

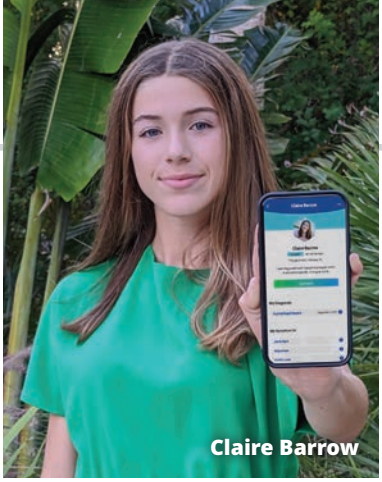
Become a Citizen Scientist

Bedrosian-Sermone's efforts also reflect the power of next-generation advocates as citizen scientists capable of changing the face of a rare disease. The Pompe disease advocate Ryan Colburn's work to collect newborn screening test results to calculate an actual incidence rate for Pompe disease showed that the widely used numbers was actually more than twice what people thought based on small and dated studies. The efforts of Chion Foundation's President and Founder Lara Pullen and TREND Community co-founder and CEO Maria Picone, parents of children with Prader-Willi syndrome, have changed the understanding of that disease. Prader-Willi is a complex genetic condition characterized by obesity, excessive hunger, low muscle tone, and developmental and intellectual disability. The work Pullen and Picone did highlighted the sleep apnea and daytime sleepiness that is associated with the condition and identified pitolisant, a recently approved drug, that had the potential to benefit these patients. Harmony Biosciences, the company that produces the drug, is conducting a phase 2 clinical study of the drug in people with Prader-Willi as a result of their efforts.



Lara Pullen

Maria Picone


Claire Barrow

Leverage Technology

Technology is changing the face of rare disease in every aspect in the diagnosis, drug development, and treatment of disease. It is also a leveling force that is giving individuals the power to participate in research, enabling decentralized clinical trials, and capturing patient and caregiver input in new ways that bring a more patient-centric approach to drug development. While the use of artificial intelligence is helping to accelerate drug development, assisting with the diagnosis of rare disease, and moving into the clinic to help guide treatment decisions, at the most fundamental level it is a communication tool that has allowed people with rare disease to participate in a global community and find others with the same condition, learn from each other, and amplify their voices. When Claire Barrow was diagnosed in 2019 at the age of 13 with the rare bone condition hypophosphatasia, she had difficulty finding information about the condition or anyone else who had it. She and her brother Hill convinced their parents that they should create an app to help rare disease patients with the same conditions connect with each other and RareGuru born. Today, it has about 2,500 users in seven countries.

Change Regulators Thinking


Jet and Christine McSherry

Drug development takes place in a highly regulated environment. Some of the most significant barriers to advancing treatments from the lab to the patient can be regulatory. Christine McSherry's son Jett was diagnosed with the rare and progressive neuromuscular condition Duchenne muscular dystrophy at age 5. As founder and executive director of the Jett Foundation, McSherry attended an FDA meeting and approached leadership at the agency about the endpoints being used in the clinical trial for Sarepta's DMD therapy Exondys 51. She was concerned that the small trial underway for antisense therapy relied on the six-minute walk test 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 on the drug were doing better but the endpoint wouldn't reflect that. Officials told her to show them and she filmed all 12 boys in the clinical study, as well as a few others who were later enrolled in a safety study, and 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's assistance. She made a two-hour presentation to the FDA. While officials were moved by the presentation, the agency said it couldn't incorporate it into the formal materials for the drug review. Nevertheless, the agency allowed her to make a 10-minute presentation to the advisory committee that reviewed Exondys 51 and at the encouragement of Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, she co-founded Casimir Trials, a contract research organization that works to analyze and report rare disease patient and caregiver perspectives and real-world evidence collected remotely.

A Membership No One Sought

Rare disease advocates often describe having a membership in a club they never would have wanted to join. For next-generation advocates, regardless of whether their efforts have saved the life of a loved one or they have suffered a heart-breaking loss, their advocacy efforts don't end: whether it's mentoring others, driving an organization forward, or working to ensure others who come behind them have treatments. For these advocates, it is a membership for life. ■

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