



NEXT 2022

Redefining
the Possible



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Contents

Introduction	
The Sound a Rare Disease Makes in a Forest.....	5
Research	
The Quest for a Cure Begins with Data.....	8
Diagnosis	
A Push for Earlier Answers	14
Development	
A Move from Patients to Funders to Collaborators.....	22
Regulatory	
Seeking Gains as New Threats Emerge.....	34
Finance	
A Good Year for Raising Money.....	42
Treatment	
Understanding the Costs of Rare Disease	52
Endword	
If a Gene Therapy is Created, Does it Cure a Patient?.....	64

A Letter from the CEO



**Craig Martin, CEO,
Global Genes**

In 2021, investors poured \$18 billion into rare disease therapeutics development, a 28 percent increase over the previous year, despite turbulent trading on Wall Street and the ongoing disruptions from the lingering COVID pandemic.

The strength of the sector was buoyed by ongoing innovation, particularly around genetic medicines and their potential to radically alter outcomes for patients with rare diseases.

Rare disease companies continue to have a strong allure to investors, and this should continue as pipelines are strengthened by emerging technologies and their growing ability to provide not only meaningful treatments for conditions with unmet needs but also address the underlying cause of genetic diseases and provide functional cures.

One continuing trend we highlight in this year's NEXT report is the migration of patient organizations beyond funding early-stage academic research, to translational research funding and even development funding to advance treatments for the conditions on which they are focused. With growing financial and drug development sophistication, organizations are sitting at the table with drug companies as true equals in forging development strategies, and in some cases launching their own companies to advance therapies that drug developers do not recognize as having commercial potential.

We know that science and drug development often move at a slower pace than rare diseases progress. We must not lose site of the urgency that defines our community and never grow complacent with our many successes. Nevertheless, the rapid pace of progress should provide hope to many.

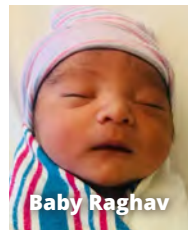
A handwritten signature in black ink, appearing to read "D. Craig Martin". The signature is fluid and cursive, written on a white background.

D. Craig Martin
CEO
Global Genes

Introduction

The Sound a Rare Disease Makes in a Forest

Hours after Sanath Kumar Ramesh's son Raghav was born in 2018, doctors grew concerned that something wasn't right. He lacked the energy to lift his hand, move his leg, or drink. After many tests, a protracted hospital stay, and a couple of misdiagnoses, physicians on Raghav's first birthday determined he suffered from sedaghatian type spondylometaphyseal dysplasia, an ultra-rare and progressive disorder.



Sedaghatian type spondylometaphyseal dysplasia (SSMD) is caused by mutations in the GPX4 gene. There are only about nine known patients with GPX4 mutations. In the past, most known cases resulted in death about a month after birth. Ramesh launched CureGPX4.org to drive research and develop a treatment for his son's condition.

Ramesh had screens performed to find existing drugs that might provide benefits to his son on an off-label basis, but his bigger hope was to have a gene therapy developed. As he sought to do that, he realized that many patients and patient organizations try to head down that same path, so he launched Open Treatments, a nonprofit that provides a software platform to provide patients and individuals seeking to develop a gene therapy for a rare, monogenic disease with the tools and technology to do so by connecting them to researchers and vendors and providing a roadmap for what they must do to get there with the hope of handing off a project to a commercial drug developer.

While running the first set of pilot programs, though, Ramesh came to realize that Open Treatments got ahead of itself. There were earlier steps in the process that are es-

sential before a gene therapy could ultimately be developed for his son's or other conditions for small populations that are not well understood.

"Unfortunately, patients like my son who are in that category are among the last people in the world that would ever get treatments because no one knows about my son's disease. No one cares about it," he said. "Bringing these diseases into the center, putting them on the map so that you don't have to be hemophilia, you can be SSMD with just nine patients, but you're just as likely to get treatment because the broader biotech and the scientific community has a means to look at your disease, pay attention to it, and evaluate it."

Being Counted

There is both a philosophic and scientific question that has been asked as to whether a tree that falls in the forest, if there is no one is around to hear it, makes a sound. The question, which has evolved through the years, was first posed by the magazine *The Chautauquan* in 1883 and appears to have been inspired by a 1710 treatise by George Berkeley, a philosopher who put forward the theory of immaterialism, a notion that something cannot exist without being perceived.¹

For rare disease, there is a practical existential question about at what point a rare disease exists. In reality, that threshold differs for patients, physicians, researchers, drug developers, and payers. A patient with a disease, no matter how rare, does not need to be convinced of

“Our mission is to create a society where every disease has at least one treatment accessible to patients, regardless of geography.”

—*Sanath Kumar Ramesh*



its existence. But for a physician to be able to diagnose the condition, for researchers to discover treatments, and for biopharmaceutical companies to develop therapies, the data and understanding of a unique disease must achieve necessary thresholds and the path to getting there and advancing along the continuum towards a cure involves data.

For many years government agencies and rare disease patient organizations have proclaimed as a statement of fact that there are 7,000 rare diseases. Some have offered a range of 6,000 to 8,000. The number has remained largely unchanged despite the also common proclamation that scientists identify about 250 new rare, genetic diseases each year. Like the tree that falls in a forest, does a rare disease without a name make a sound? If a disease is not even counted, what hope is there for a diagnosis, treatment, or cure?

When people speak of the total number of rare diseases, they are deriving these numbers from one or more various databases of rare diseases. These databases each set standards for inclusion criteria under which they will add a disease. They may rely on phenotypic descriptions, or genotypic descriptions, or both. The Mondo Disease Ontology is an effort that is working to harmonize the various rare disease databases, which sometimes overlap and sometimes conflict. In some cases, it has found one disease counted as different diseases from database to database. In another case, it has found diseases with different names from one database to another database are actually the same disease. The multi-institutional effort is trying to address the lack of a unified disease terminology to provide a comprehensive harmonization of the world of rare diseases.

A forthcoming study from the nonprofit collaborative rare disease data sharing platform RARE-X offered a new perspective on the question of how many rare diseases are unacknowledged today and inadvertently created a roadmap for patient advocates seeking to move a rare disease from obscurity to cure. The study sought to address the peculiar lack of change in the total number of rare diseases. In doing so, the authors divided the world of rare diseases into

categories. It found that there are as many as 10,869 rare diseases including both genetic and non-genetic diseases, as well as rare cancers. For their study, the authors divided the world of rare diseases into four distinct buckets: conditions for which a treatment is available, conditions that are considered diagnosable because there are genotypic and phenotypic descriptions (even if more research is needed), conditions that are poorly defined, and conditions that are not currently recognized in major databases. Of those buckets, 488 rare conditions have approved treatments, 8,512 are diagnosable, and 2,357 are poorly defined.

When a disease that is below the radar is discovered, the goal for advocates is to move it through the progression from being poorly defined, to diagnosable, and ultimately to a point where there is a treatment. To do that requires lowering the bar for scientists by creating funding to do the research necessary to define a rare disease clearly enough in a peer-reviewed study to make its way into one of the existing databases of rare diseases. It requires finding other patients with the same condition and gathering data for natural history studies and patient registries. And at that point, work on therapeutic discovery can begin with the hope of moving that far enough that a drug developer would be willing to step in with the belief that there are enough patients with the condition and that new patients can be diagnosed so that should a therapy reach market, it could be commercially viable.

There is a continuum. At the individual disease level, it provides a path for advocates to think about as they seek to take a newly discovered disease and move it to a recognized condition that can be treated and diagnosed. A name for a disease makes it more likely to be diagnosed. Diagnosed patients make it more likely that there will be data collected about the condition. Data leads to understanding of a disease. Understanding of a disease leads to treatments. But to repeat again and again that there are 7,000 rare diseases is to deny the magnitude of the challenge of finding a diagnosis, treatment, and cure for the nearly as many rare diseases that lack even the simplest acknowledgment of their existence.

Putting a Disease on the Map

That's been a painful lesson for Ramesh in his efforts to develop a gene therapy for his son Raghav's condition and provide a platform for others to do the same. Ramesh figured he would need to raise between \$5 million to \$7 million to advance a gene therapy to a point where it could move into human clinical trials. He believed at that point, it would be easy to get a pharmaceutical company to take over development.

He said while there have been some patients who defied the odds to raise that kind of money, he began to see it as a tradeoff between how much time he wanted to spend on fundraising versus how much time he would get to spend on his son who was suffering from a progressive disease. As he spoke to various biotech companies about whether they would be interested in funding a gene therapy for GPX4, he quickly learned that there would not be an interest.

As he spoke to patient foundations, especially the ones that represented small patient populations of 100 to 1,000 patients, he began to see them falling into one of two categories. The first were organizations that had made exceptional progress and raised millions of dollars to advance a gene therapy program into the clinic. They may have even seen a few patients with those conditions dosed in a clinical trial. When they went back to a potential biotech partner to hand off their programs, however, Ramesh said they often discovered there were challenges in the company's ability to take over the programs, which may have had to do with experiments that had not been done properly, the wrong choice of vector, or that the program was not going to fit in with the platform technology that company was focused on. Despite the funds that had been invested, he said these programs are left on a shelf and are not getting to patients who could benefit from them.

The second group, he found, were ones where there were about 500 patients worldwide, but there was no unifying voice, no driving force behind them. They had some animal models

developed, but they had not gotten research studies started, even though, in theory, a gene therapy would be a good fit for them.

"After seeing these two cohorts of patient foundations, it was clear to me that the noise that we are hearing from the industry around SMA getting treatments, progeria getting treatments, and so many other rare diseases, is awesome and motivating," said Ramesh. "But there are thousands of diseases that are never going to make it beyond the cut line unless we do something about it."

He said Open Treatments was conceived as a platform to decentralize drug development and provide a roadmap to organizations and individuals who want to pursue the development of a gene therapy. But now, he said, he realizes the lack of disease awareness and lack of funding that still must be addressed. As a next phase of Open Treatments, he said he is now addressing the more fundamental issue of making invisible conditions and invisible patients visible and will work to create a map of the rare disease world. As of this writing, the new effort by Open Secrets was a work in progress.

"We're not building a registry platform. We are not building a natural history platform. We are simply a gateway to getting to essentially connect patients with their respective communities," he said.

The hope is that in so doing, a picture will emerge of the landscape of rare disease, the prevalence of a condition, and a catalogue of such things as animal models, cellular models, and data for each of these conditions. Individual patients could enter the data themselves and the rare disease community would collaboratively add and edit information in this vision of a Wikipedia of rare diseases.

"Our mission is to create a society where every disease has at least one treatment accessible to patients, regardless of geography," said Ramesh. "We always look for ways we can solve this problem." ■



The Ramesh family

The Quest for a Cure Begins with Data



“The urgency and the demand for all of this information, which has been missing for quite a long time, is now coming to a head.”

— Nancy Yu, co-founder and CEO of AllStripes

Stella Linderman had been a healthy infant during her first five months of life as she developed as expected. But on April 13, 2020, Stella had her first seizure. Two weeks later, early in the COVID-19 lockdown, a doctor delivered news to Stella’s parents Greg Linderman and Jessica Mandelbaum over an online video chat that their daughter had a rare genetic condition known as CDKL5 deficiency disorder. “That’s where our whole world changed,” said Mandelbaum.

CDKL5 deficiency disorder is a developmental epileptic encephalopathy caused by mutations in the CDKL5 gene. In the case of Stella, the mutation was *de novo*, and not passed down from her parents. The condition is characterized by early onset and causes intractable epilepsy and neurodevelopmental delay impacting cognitive, motor, speech, and visual function, according to the International Foundation for CDKL5 Research. Though rare, it is one of the most common forms of genetic epilepsy.

Linderman, a Top Gun-trained navy pilot now in the reserves, took on the daily care of Stella, dealing with her seizures, getting her therapies and nursing care, and

seeking out financial aid. Jessica, along with her parents Joe and Nancy Mandelbaum and her brother Greg, took to the Internet and began contacting patient organizations and researchers, and doing anything else they could to find treatments for Stella. The Mandelbaums work in a family real estate tax and investment advisory service and appreciate the value of data in what they do. As such, an early focus for the family has been to get Stella’s medical information into the hands of researchers.

Within days of her diagnosis, her grandfather Joe was in touch with researchers and CDKL5 communities in Australia, the United Kingdom, and the United States. He said his searching found half a dozen places where people were collecting data about CDKL5 deficiency disorder patients from caregivers. While the family said they were more than happy to share Stella’s information wherever they thought it might do some good, there were too many databases and not enough synergy between them.

The family’s search for how to best help Stella became an education in the data landscape for rare diseases. They found themselves quickly schooled about the need for good collections of data to entice drug companies to invest



Stella Linderman



Jessica Mandelbaum and Stella



Greg and Stella Linderman

in the development of therapies for a given disease, but they also found data locked in silos, often redundant, and incapable of providing the guidance they sought for how to best address Stella's seizures and what abilities she would have. Wanting to do whatever they could to help Stella and advance the understanding of her condition, they began to share her data with various data collection efforts.

"We appreciate and are very happy that so many different organizations and people are studying CDKL5 and looking into CDKL5, but so many of these questionnaires ask such similar questions and take the same amount of time. And it's a lot of time," said Jessica Mandelbaum, who said while she's happy to do anything to help her daughter, she is frustrated by the inefficiency. "On top of it being a lot of time, it's an emotional toll. With a lot of these questions, you just have to relive what your child has over and over and over again."

The problem for Stella's family was not just that data was spread in so many places, but the data they needed to make informed decisions about how to best care for Stella either didn't exist or was not accessible. Despite the fact that researchers in various places were studying CDKL5, the family was shocked to discover how little was actually known about the population of people with the condition.

While there were estimates about the size of the population of people with CDKL5 mutations, no one knew the actual number. What's more, no one could tell the family how many of the children with the condition could walk, or what percentage of patients had benefit from a given medication.

"When we were first diagnosed, we were thrown in the deep end. We had to make a lot of decisions very quickly to try to get Stella's seizures to stop. And we had to make those decisions based on people's educated guesses, but it wasn't based on facts. It wasn't based on figures," said Jessica Mandelbaum. "Knowing what I know now, I would not have tried some of the very harsh medicines that we initially tried at the beginning, because I now know they really wouldn't have done anything, but it would have been helpful to have a database to show me the figures and I could have decided."

She said in the absence of available data, all the family could turn to for such answers were other parents and caregivers on Facebook support groups. While these support groups were good for certain things, Mandelbaum said they were filled with lots of emotion and little in the way of information. "I don't want the emotion. I want to know, did this work? Did it not work? Did it lessen seizures, or did it stop seizures, or did it increase seizures?" she said. "I just want to know the facts."

"With a lot of these questions, you just have to relive what your child has over and over and over again."

—Jessica Mandelbaum

Patients Take the Initiative

Patients and caregivers seeking treatments for a rare disease where no approved therapies exist have become directly involved in the drug development process. Patients and caregivers have come to recognize that in order to engage academic researchers, entice pharmaceutical developers, and pursue the discovery and development of new therapies requires data. At the most basic level, this includes the need for patient registries and natural history studies as they are critical to finding patients and unlocking an understanding of a rare disease, identifying its manifestations and course of progression, and determining meaningful endpoints for clinical studies.

“Early on, one of our scientific advisory board members, who runs a biotech company, told me if you do one thing, conduct a natural history study. That is something that is difficult for biopharma to do. It’s hard for biotech companies to access patients and contact patients, but as an advocacy group we can do that,” said Nasha Fitter, co-founder and CEO of the FoxG1 Research Foundation and director of rare neurological diseases for the patient data platform Ciitizen. “I took that to heart and plunged into how we collect good data. There were mistakes we made along the way. We started a registry and we created our own survey, and then later I learned that if it’s not an FDA validated survey, that information is useful internally but won’t be taken seriously. We had to start over and get validated surveys.”

As patient organizations have driven deeper into data collection, they have grown more sophisticated about their efforts and have recognized it’s not enough to collect data, but that it must be done with an eye towards standards and governance and be rigorous enough to be used by drug developers and regulators.

Patient advocates who have grown frustrated by finding that their data is in the hands of entities that may be either unwilling or unable to share it with others who might advance their quest for treatment, have grown weary of having to duplicate data gathering efforts

rather than leveraging them. As such, before engaging in data collection efforts, they have begun to ask questions about ownership and data sharing with an eye toward not just current uses, but potential future uses as well.

In 2021, several data collection efforts built around patient-owned data gained attention in the world of rare disease as these various initiatives achieved significant milestones. The developments reflect the growing activity to create platforms to empower patients to leverage their own data to advance research while allowing them to retain control over who has access to their data and how it can be used.

“There’s been a lot of need for engaging patients in their own care and drug research, and relying on and partnering with communities directly to understand what’s important to them in drug clinical development, as well as the level of evidence that is now needed to support different drug programs in terms of trial design, supporting FDA submissions, and a whole host of other things that are needed to get a drug across the finish line,” said Nancy Yu, co-founder and CEO of the healthcare technology company AllStripes. “The urgency and the demand for all of this information, which has been missing for quite a long time, is now coming to a head. That’s really driven by a lot of the science that has come to market.”

In August 2021, AllStripes, formerly known as RDMD, completed a \$50 million series B venture round, which it said will allow it to onboard an additional 100 rare disease research programs while expanding its global footprint, enhance its technology, and expand the capabilities of its patient data platform. The financing follows AllStripes’ expansion of its research programs to the United Kingdom early in the year, its first outside North America.

The Rare Disease Cures Accelerator-Data and Analytics Platform initiative (RDCA-DAP) in September launched a new phase of its data platform. The RDCA-DAP, created through a partnership between Critical Path Institute and the National Organization for Rare Disorders, is an initiative funded by the U.S. Food and Drug Administra-

“Early on, one of our scientific advisory board members told me if you do one thing, conduct a natural history study.”

—Nasha Fitter



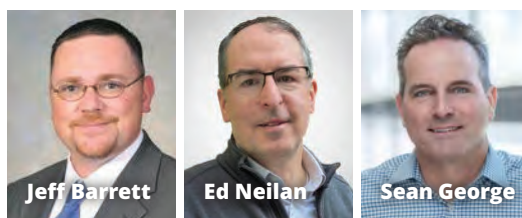
tion. It was created to provide a centralized and standardized base to host and share de-identified data to support treatment innovation.

“It is not just about the data. This is a place to generate solutions in a highly collaborative way,” said Jeff Barrett, C-Path senior vice president and RDCA-DAP lead. “We expect RDCA-DAP to be a place to promote candid dialogue, optimize patient selection and trial design, and co-develop the tools to further de-risk decision making for rare disease drug development.”¹

RDCA-DAP hopes that by making data available to researchers and drug developers, diseases that might otherwise be overlooked can get the attention of industry. “Patient-owned data collected by patient groups are less likely to get stuck in a silo,” said Ed Neilan, chief medical and scientific officer of NORD, who noted only a small percentage of rare diseases have approved treatments or are the subject of industry drug development efforts. “RDCA-DAP may bring attention to rare diseases that might otherwise remain relatively neglected.”²

The medical genetics company Invitae in September 2021 announced it would acquire the health technology company Ciitizen, which is building a global platform to help patients collect, organize, and share their medical records, for \$325 million in cash and stock. The deal will enable Invitae to combine genotypic with phenotypic data about patients.

“Genomics is currently a laboratory testing-based industry, but in the future, it will look very much like an information industry,” said Sean George, co-founder and CEO of Invitae. “Developing an open-ended patient-centric



platform of genomic, clinical, and reported outcomes creates a thriving and purposeful network that truly advances healthcare.”

RARE-X, a nonprofit federated rare disease patient data platform that is leveraging technology developed by the Broad Institute of MIT and Harvard, launched its initial set of 11 pilot data collection programs in July 2021. The 11 programs involve an international group of 17 organizations with plans to have 100 patient organizations and data from 100,000 patients onboarded on its platform by the end of 2022. The initial set of pilots involve neurodevelopmental conditions with the hope that researchers will be able to learn more by looking across conditions rather than by looking at individual conditions in isolation.

“The ultimate hope is that there are commonalities and patterns in the aggregate datasets that go beyond the 4H community. It’s important to us that we, as a rare community, don’t sit in silos,” said Christina Butterworth, executive director of the rare disease patient advocacy organization Yaya Foundation for 4H Leukodystrophy, a rare neurodevelopmental disease. “What’s really compelling about RARE-X is that we get to combine, standardize, and make 4H data accessible on a platform for rare disease data sharing in the hopes of advancing, and even accelerating, discovery, diagnosis and treatments for the 4H community and beyond.”

“The ultimate hope is that there are commonalities and patterns in the aggregate datasets that go beyond the 4H community.”

—Christina Butterworth



Global Genes, publisher of this report, entered into a partnership in October 2021 with RARE-X to help patient organizations leverage their data to drive research and drug development. As part of the collaboration, RARE-X will build data-collection portals for interested patient communities, and work in partnership with Global Genes to educate, train, and provide ongoing support to ensure patient communities get the most out of their data collection efforts.



Silo-Busting or Just Making New Silos

While the proliferation of platforms to gather patient-owned data should help drive research, there is concern that rather than busting silos there's a risk that these efforts might just be erecting new ones. In a position statement published in April 2021 in the *Orphanet Journal of Rare Diseases*, Nathan Denton, scientific communications manager for the Gene Therapy Program at the University of Pennsylvania, and his co-authors warn that balkanization of data through use of proprietary forms for databases, along with economic and academic incentives, undermine the effort to develop new therapies by fragmenting knowledge. The lack of coordination leads to redundant data collection and duplicative studies that ultimately delay the development of needed therapies. The authors say that the current system also encourages wasted time, energy, and resources.

They argue that data silos, exclusive access rights, and reluctance to share data represent some of the biggest threats to progress in rare disease drug development. While they note that there has been some success, they say the current biomedical research and development ecosystem fails to fulfill its potential.

Though the situation is by no means limited to rare disease research, its consequences are worsened by the challenges inherent in developing drugs for small populations that are geographically dispersed and suffering from conditions that are heterogeneous in nature. The lack of good quality data and natural histories make it difficult to develop meaningful outcome measures. The authors argue that the combination of advances in genomic technologies and information technology makes it critical to bring stakeholders together to reach agreement on key issues relating to registry design, data sharing, and data governance. They say while groups at the National Institutes of Health and the U.S. Food and Drug Administration have started programs to address these issues, they believe more discussion of how to coordinate and scale registry efforts is needed.



“Technology and open data rules (including meaningful use regulations requiring interoperability and patients’ ability to share their electronic medical records) are democratizing registries such that many patient communities have initiated registries and deployed data collection tools, including wearable sensors, apps, and social media channels,” they write. “Rare disease ‘umbrella’ groups (that is, those that work across many rare diseases) have initiated larger registry and data initiatives (for example, see programs by NORD, Rare-X, and RDCA-DAP), which further expand the registry ecosystem. While we applaud these efforts and their intent, the rapid expansion of registries is poised to exacerbate data loss, replication, and/or data gaps without standard practices changing among stakeholders.”

RARE-X, which is leveraging technology to connect disparate data sources and enable data sharing technology through a federated data platform, said it has been working with standards organizations to ensure the organization is addressing these problems rather than just creating a new one.

As part of the critical issues to enable data sharing, RARE-X spent 18 months on developing a consent process that not just considers an anticipated use for which the data is being collected but potential future uses, while leaving patients in control of whether and with whom they want to share their data. The problem is that consent agreements have traditionally been created to serve the legal and ethical review requirements of the institutions collecting the data rather than ensuring the use of the data is maximized.

“One of the reasons that data gets siloed is because when the participant consented for the

“It’s more policy and procedures. It’s not conducive for a hospital to share. They don’t generally get revenue off sharing data.”

—Jason Colquitt



use of that data, there was only the immediate usage contemplated. That means that it's essentially siloed for usage beyond that initial study, which is a disservice to that participant's efforts and the information that they've shared, whether it be through a survey or whether it be bio samples, et cetera," said Charlene Son Rigby, CEO of RARE-X. "That's one structural thing that we are really looking to change—to enable through the consent maximizing the utilization of data in a secure and appropriate way."

Culture, Not Technology, is the Barrier

Jason Colquitt, CEO of Across Healthcare, which develops technology for healthcare providers and patient organizations, tells the story of suffering a heart attack at one of his local hospitals. He received care from a hospital that's different than where his cardiologist works. Even though both hospitals use the same electronic health record platform, he said it took six months for his cardiologist to get his records from the other hospital. Colquitt points to his own experience to say there are a number of barriers to data sharing and enabling patient data to be used to its full potential, but he doesn't count technology among the major obstacles.

"It's not that there aren't technology hurdles, but they are achievable. It's more policy and procedures. It's not conducive for a hospital to share," he said. "They don't generally get revenue off sharing data. I can only assume it becomes a lower priority for them."

He said much of the issue lies in convincing all of the people who have data that they should share it. In some cases, they may be prohibited from doing so due to narrowly conceived consent agreements. In other cases, they may choose not to share their data for competitive or other reasons.

Federated data systems like RARE-X connect disparate databases and allow the data owners to share their data through a common interface, but keep the data stored on the data owner's own platform and leave the data owner in control of who can access it.

Nicole Boice, co-founder of RARE-X, said the technology is already in place to enable data sharing and collaboration. "It's not about the technology. The technology is there," she said. "It's about behavior change. It's about trust. It's about ensuring that we can create an ecosystem, an environment that gets everyone what they need to get that ball across the goal line."

The other challenge that remains is to convince patients and their families about the critical need for sharing their own data. While many patients or their caregivers may be motivated to share their data and understand the critical role it plays in making medical advances, others are concerned about the security or privacy of their data, or may feel overwhelmed by the demands some data collection efforts place on their time.

Mike Graglia, managing director of the SynGAP Research Fund, a patient organization working to support research and development of treatments for the rare neurodevelopmental condition SYNGAP1-related non-syndromic intellectual disability, was early to embrace the Citizen platform. He's been working to leverage that through a collaboration with other organizations involved in driving research in other rare neurodevelopmental conditions in an effort backed by the Chan Zuckerberg Initiative.

He said it takes just 10 minutes for a patient to sign up on Citizen, which then does all the work of gathering health records from providers and formatting their data. He said the hard work for patient organizations has been to engage and recruit the participation of patients and their families who often have fears of compromising their privacy, or that a data gathering service or drug company is seeking to profit off their health information without understanding the essential role it can play in advancing towards treatments.

"There are some parents out there who just don't get it. There are people who are inherently distrustful of research. There are people who don't know how this data is going to be used," he said. "They're stuck on privacy, and they've missed the memo that their kid has a rare disease and privacy is the least of their worries." ■

"It's not about the technology. The technology is there. It's about behavior change. It's about trust."

—Nicole Boice



Diagnosis

A Push for Earlier Answers



“If you don’t have the diagnosis, you can’t have the treatment to prolong your life and to eliminate those things from potentially ever happening.”

— Tia Jones, founder of Testing for Tots

In May 2018, two weeks before Brian Jones graduated from medical school, he learned about a disease he had never heard of during his medical education. Jones, who was 28, was diagnosed with Fabry disease, a rare, lysosomal storage disorder caused by a genetic mutation that results in an enzyme deficiency. In the absence of adequate enzyme needed to metabolize fats, fat deposits accumulate in cells throughout the body and cause progressive damage to organs including the kidneys, heart, and cerebrovascular system. After his diagnosis, Jones encourage family members to get tested and six of his relatives learned that they too had the condition.

The experience inspired Jones to become involved in advocacy to provide access to affordable treatments for the condition. But his wife Tia was frustrated that her husband wasn’t diagnosed earlier so he could have taken steps to avoid damage to his kidneys. As they learned more about the disease, it became clear that many patients remained undiagnosed until the disease progression caused significant damage. In fact, as many as one in 300 people on dialysis today are thought to have Fabry disease.

The couple launched Testing for Tots, an initiative to ensure newborn testing performed from state to state included a test for Fabry disease. Though there have long been treatments for Fabry disease, only seven states include it on their newborn screening tests.

“When we were diagnosed, Brian’s nephrologists said to us, ‘I’ve never seen anyone with this disease who was not in kidney failure.’ The risk is that if you don’t know you have the disease, you can’t get the treatment to prevent kidney failure, to prevent strokes, to prevent heart attacks.” Tia Jones said. “If you don’t have the diagnosis, you can’t have the treatment to prolong your life and to eliminate those things from potentially ever happening.”

An Odyssey to Avoid an Odyssey

Newborn screening varies from state to state, but the U.S. Department of Health and Human Services issues a recommended list of conditions for inclusion on newborn screening known as the Recommended Uniform Screening Panel. Testing for Tots is working to fund research to compare the different testing methods used in the states that screen for Fabry disease. The effort represents one of a range of approaches from patient organizations,

academic researchers, care providers, and industry seeking to reduce or eliminate the diagnostic odyssey patients with rare diseases can face in their search for answers. Whether using genetics, biomarkers, or phenotypic information, improved understandings of rare disease and the advances of technology are accelerating the speed at which individuals with rare diseases can be diagnosed. While the ability to diagnose rare diseases is improving, the value of tests and technology need to be validated and shown to be cost-effective before they can be integrated into clinical care and bring benefits to patients.

Consider Duchenne muscular dystrophy, a condition that is among the most prevalent rare diseases and for which there are treatments. The patient advocacy organization Parent Project Muscular Dystrophy in October completed a two-year recruitment to screen more than 37,000 babies for Duchenne muscular dystrophy in New York State. The study, which included partners from the National Institute of Child Health and Human Development, and the New York State Department of Health, identified four infants with Duchenne or Becker muscular dystrophies and identified one female who was a carrier for the condition. The test was funded by a pre-competitive consortium of therapeutic developers working to bring new treatments to market for Duchenne.

PPMD called the pilot a “major step” in the effort to bring newborn screening for Duchenne and Becker muscular dystrophies as part of the process for nominating the screening test to the Recommended Uniform Screening Panel. The data is being analyzed to determine the most accurate way to screen babies.¹ The goal of PPMD’s Newborn Screening Pilot, a seven-year effort so far, is to “prevent families from experiencing an unnecessary diagnostic odyssey and ensure that every family receives timely, supportive, accurate resources and clinical care at the time of diagnosis.”

While there is a growing pipeline of experimental therapies for Duchenne, as with other progressive diseases, it is critical to intervene as early as possible in order to ensure the best outcomes.

ILLUMINA and Genetic Alliance Launch Global Initiative to Expand Access to WGS

Sequencing giant Illumina and the global nonprofit Genetic Alliance unveiled the iHope Genetic Health program aimed at providing whole-genome sequencing to patients across the globe impacted by genetic disease.

At least half of iHope Genetic Health’s efforts will be focused on areas of the world in need outside the United States with more than one-third of Illumina’s support being dedicated to patients in Africa.

Through the program, Illumina will enable Genetic Alliance to create networks of clinics, and laboratories equipped with the necessary genome technology to provide precision genomic diagnoses to patients suffering from rare genetic disease. As part of the program, Genetic Alliance will also partner with pharmaceutical and technology companies, and care providers to support patient access to data, therapeutic interventions, and ongoing supportive care.

iHope Genetic Health will build upon the success of Illumina’s existing iHope efforts, further extending the reach of the program and enabling clinical laboratories and care centers throughout the world to test patients impacted by rare disease and other genetic health conditions.

To ensure support for patients throughout their journey, iHope Genetic Health will be supported by a network of disease advocacy, technology, pharmaceutical, and clinical support organizations.



Ryan Taft

“We have a moral imperative to help genetic disease patients who need a diagnosis,” said Ryan Taft, Illumina’s iHope

lead and vice president of scientific research. “iHope Genetic Health will change the trajectory of genomic medicine worldwide, helping patients who may have otherwise been invisible. Our vision is a genome for every patient that needs one, and a network of partners who will help them on every part of their journey to better health.”

"It is the goal of PPMD and the Duchenne community to help eliminate the diagnostic delay, the two or more painful, expensive, and uncertain years that many families experience," said Pat Furlong, founder, president, and CEO of PPMD. "Newborn screening is the most effective way to ensure that infants with Duchenne are diagnosed early, when therapies will likely be the most beneficial."



increasing speed at which whole genome sequencing can be used to make a diagnosis, Rady Children's Institute for Genomic Medicine said it had set a new record for using the technology to diagnose an infant with a rare metabolic condition.

The Institute worked closely with the sequencing company Illumina and the pharmaceutical company Alexion to engineer and optimize a seamless process to decode human genomes.

Improving the Pace of Diagnosis

When conditions are not detected at birth, people with rare diseases often face a long diagnostic odyssey. Whole genome sequencing has emerged as a promising tool for diagnosing rare genetic diseases. As the cost of whole gene sequencing has fallen, and the speed of analyzing the data has increased, its practicality as a clinical tool has grown. In a demonstration of the

In June 2021, the state-funded Rapid Precision Medicine program Rady leads reported in a letter published in the *New England Journal of Medicine* that it took 16.5 hours after they obtained a blood sample and just 13 hours after initiating sequencing to diagnose an infant with thiamine metabolism dysfunction syndrome 2.² Such use of rapid genome sequencing is being pursued in Australia, England, Germany, Wales, and in Medicaid pilot programs in California, Florida, and Michigan.

Whole Genome Sequencing Enables Rare Disease Diagnoses

The integration of large-scale genomics into the healthcare system in the Stockholm region of Sweden has resulted in the diagnosis of more than 1,200 people with rare diseases, a new study reports.³

Despite the advances in whole genome sequencing technology, few clinics worldwide routinely use it to diagnose patients. The report, published in *Genome Medicine*, adds to the case for the value of whole genome sequencing as a clinical tool. The study from Karolinska Institutet in Sweden

analyzed the result of the first five years of a collaboration on whole genome sequencing between Karolinska University Hospital and SciLifeLab.

It found during that time, the center carried out genome sequencing of 3,219 patients, which led to molecular diagnoses for 1,287 patients (40 percent) with rare diseases. The researchers found pathogenic mutations in more than 750 genes and discovered 17 novel disease genes. In some cases, the findings have enabled personalized treatment for patients with, for example, inherited metabolic diseases, rare epilepsies, and primary immune deficiencies. An effort is now underway to broaden the approach in the Swedish healthcare sector.

"Used in the right way," said Anna Wedell, professor at the

Department of Molecular Medicine and Surgery at Karolinska Institutet, and one of the paper's corresponding authors, "targeted at each patient's specific clinical situation, new groups of patients can receive the right diagnosis and treatment in a way that hasn't been possible before."

Because there is a need to manage and interpret the millions of genetic variants that exist in each individual, the center said it has developed a model that directs the initial analysis to pathogenic variants in genes deemed relevant for each patient's clinical symptoms. This requires doctors to play an important role in deciding which genetic analyses should be done first. If the first assessment fails to produce a result, the analysis is broadened to more gene panels until a diagnosis can be established and/or the whole genome is sequenced.

The patient, a 5-week-old male infant who had been previously healthy, was admitted after two hours of crying and irritability that was out of character for him. No matter what the parents did, they were unable to calm him. A CT scan revealed the child had abnormalities. His parents, who are first cousins, had a child ten years earlier who had died at the age of 11 months from an epileptic encephalopathy, but no specific diagnosis was made. Infantile encephalopathies are associated with about 1,500 genetic conditions, and though they present in a similar manner, the researchers said many have unique and effective treatments. Without prompt treatment, permanent neurologic injury or death occurs in many infants with these diseases. A misdiagnosis can result in inappropriate or delayed treatment, they said. Two hours after the diagnosis, physicians began treatment. The child suffered one, 15-second seizure after that, but six hours later he was alert, calm, and feeding from a bottle. He continues to do well.

“This case illustrates the potential for decreased suffering and improved outcomes through the implementation of rapid genome sequencing in a multidisciplinary, integrated, precision medicine delivery system,” the researchers wrote in the letter. “Such a system includes identification of infants with suspected genetic diseases on the day of admission, rapid genome sequencing as a first-tier test, communication of results in a manner that facilitates prompt transition from empirical to etiologically informed treatment, and implementation within a learning healthcare system.”

Since the fall of 2020, when Rady Children’s sequenced the first child under its accelerated research protocol, it has sequenced a total of seven patients in less than 14 hours using the same process. Three involved critically ill patients admitted to intensive care at Rady Children’s Hospital-San Diego. Another four were retrospective cases.

While the ability to diagnose patients with rare genetic diseases has improved with whole genome sequencing, it remains an imperfect process. In fact, experts estimate that in more than half the cases, the use of whole genome

sequencing will fail to deliver a definitive diagnosis. That can be due to a number of reasons including the inability to discern the genetic mutation causing the disease from all of the mutations present in the genome, the lack of a known association between the causal mutation and a rare disease, or because the cause of the condition is not genetic in nature.

“We’ve seen a strong push in the last 10 or 15 years in identifying new disease genes,” said Matthew Bainbridge, associate director of clinical genomics at Rady Children’s Institute for Genomic Medicine. “If a kid has a mutation in a gene that isn’t currently associated with a disease, we can’t diagnose that child until we’ve done the research and can establish the association between mutations in the gene and the disease that the kid has.”

Going Long

Technological improvements are helping to diagnose previously undiagnosed patients. Bainbridge is principal investigator on a study Rady Children’s Institute for Genomic Medicine is collaborating on with Pacific Biosciences of California to identify potential disease-causing genetic variants to improve the diagnosis of rare diseases. Through the collaboration, the two partners are using Pac Bio’s HiFi, long-read, whole genome sequencing on patients for whom short-read whole genome sequencing and exome sequencing failed to provide a diagnosis.

Bainbridge likens short-read sequencing to reading a book one sentence at a time compared to long-read sequencing, which is like reading a page at a time. While short-read sequencing can reveal the equivalent of a typographical error—the misspelling in a gene sequence—long-read sequencing can help distinguish between pseudogenes (sequences that resemble genes but are non-functional because they appear in non-coding portions of the genome) and actual genes by providing greater context to the aberrant code depending on whether it appears in a coding or non-coding region of the genome.

“We’ve seen a strong push in the last 10 or 15 years in identifying new disease genes.”

—Matthew Bainbridge



“We want to take kids from the back of the line and put them at the front.”

—Tom Curran



The study, which is currently underway, has already been able to detect variants that were not identified by short-read sequencing. Of these newly found variants, an average of 37 were so-called “missense” mutations in known disease genes. Missense mutations involve the change of a single base pair that results in the substitution of an amino acid in the protein for which a gene codes and can render it non-functional.

Bainbridge said long reads have also proved useful in identifying structural variants. He said if a standard variant is like a typographical error in a book, a structural variant might be akin to ripping out three chapters from a book, turning them upside down, and reinserting them back into the book. “These kinds of big structural variants are often mediated by these repetitive elements. So, there are these two pages that are very identical. That’s what the structural variant actually relies on—that identicalness to cause the inversion—or the ripping out and the replacing,” he said. “It’s not always easy to actually tell that’s happened when you’re only reading a sentence at a time. When you’re reading multiple pages, it’s much easier.”

Children’s Mercy Kansas City also expanded its use of whole genome sequencing using PacBio’s HiFi sequencing to identify potential disease-causing genetic variants and increase the rate of solving cases of children with undiagnosed rare diseases. It began working with PacBio’s long-read whole genome sequencing of rare disease cases for which previous short-read whole genome and exome sequencing studies yielded no answers. That study has already resulted in the detection of multiple new diagnoses, including a novel expansion disorder, precise definition of breakpoints and orientation of structural and copy number variants, and the identification of novel inversions.

“It gives a very different kind of product that allows you to look at fairly large-scale gene rearrangements, which are often missed in the more standard whole-genome sequencing approaches,” said Tom Curran, senior vice president, chief scientific officer, and executive director of the Children’s Mercy Research Institute. “We do believe that this technology still has ways to

develop and grow, but we want to be in on the ground floor pioneering its application for these children in need. We want to take kids from the back of the line and put them at the front.”

Mercy Children’s Research Institute is in the midst of an ambitious effort to sequence 100,000 genomes—30,000 children and their siblings and parents—through its Genomic Answers for Kids (GA4K) program. In October 2021, the institute as part of that effort released more than 2,900 pediatric rare disease genomes through the program, what it described as one of the largest pediatric rare disease whole genome datasets ever publicly shared. More than 3,160 patients with rare diseases have enrolled in the program and as of October 2021, it said it had provided 586 genetic diagnoses.

Data sharing is an essential part of the GA4K program. The GA4K pediatric data repository is collecting genomic data and health information and making the full pediatric data repository available in real-time to researchers and clinicians. The GA4K program also periodically deposits full raw sequence data of patients and family members, which is accessible through the National Institutes of Health dbGAP database.

Tomi Pastinen, director of the Genomic Medicine Center at Children’s Mercy, said everyone speaks supportively of data sharing, and the funding agencies mandate it to some extent, but there is a culture of secrecy in the life sciences that lingers from the past due to competitive concerns. He said a cultural shift is needed to get people to stop hiding behind genomic privacy.

“You wouldn’t be able to put out the sequence. You were afraid that someone else will publish your gene first,” he said. “We’re way past that



Study Shows Whole-Genome Sequencing Improves Care of Critically Ill Infants

Use of clinical whole-genome sequencing outperforms usual care by two-fold both in terms of diagnostic efficacy and change of clinical management of acutely ill newborns suspected of having a genetic condition, according to a study published in *JAMA Pediatrics*.⁴

The study, conducted by scientists at the sequencing company Illumina and researchers at five children's hospitals across the United States, supports the widespread adoption and implementation of clinical whole genome sequencing for newborns in crisis.

Researchers randomized the patient population of 354 infants to either receive cWGS within 15 days (Early arm) or 60 days (Delayed arm) of admission, with

a total observation period of 90 days. In both arms of the study, access to clinical whole genome sequencing doubled the proportion of patients receiving a precision diagnosis of their condition and a change of clinical management.

At 60 days, twice as many infants in the early group vs the delayed group received a change of management and a molecular diagnosis. At 90 days, the delayed group showed a doubling of change of management. The most frequent changes of management across the observation window were subspecialty referrals (11 percent), surgery or other invasive procedures (4 percent), condition-specific medications (2 percent), or



Chester Brown

other supportive alterations in medication (3 percent). No differences in length of stay or survival were observed.

“The NICUSeq study has shown us the importance of large-scale genetic testing in newborns, leading to early diagnosis of genetic conditions and helping to inform decision making for physicians and families,” said Chester Brown, Genetics division chief at Le Bonheur Children's Hospital and the University of Tennessee Health Science Center. “Having this type of genetic information provides immediate and sustainable benefits that have lifelong value, providing a genetic ‘report card’ that can be used to help direct medical care throughout life.”

stage and the public genomics programs, starting with the Human Genome Project, but then multiple other variation discovery programs have paved the way to show that by sharing, you advanced the science quickest.”

The Promise of AI

While whole genome sequencing gets much of the attention, the use of artificial intelligence and machine learning has become an essential component of identifying pathogenic genetic variants underlying rare diseases. Beyond the analysis of genomic data, the power of these computing technologies is being used to analyze other types of data ranging from electronic health records to images of the faces of patients to detect patients who may have a rare disease.

For instance, researchers at the Feinberg School of Medicine, Pfizer, and elsewhere reported in

a May 2021 study published in *Nature Communications* that by applying a machine-learning model to electronic health records, they could identify patients at risk of the rare condition transthyretin amyloid cardiomyopathy (ATTR-CM). The condition, which can cause heart failure, is underdiagnosed, and requires different treatment than other forms of heart failure. The researchers analyzed a database of medical claims data to create a machine learning model that could be applied to electronic medical records to identify patients who may have ATTR-CM.⁵ Researchers are now testing the accuracy of their model by applying it to patients at Northwestern and hope to see it eventually integrated into electronic health record platforms.

ThinkGenetic, which developed FindEHR, uses artificial intelligence to identify patients with an undiagnosed rare disease. It uses a proprietary algorithm that scours electronic health records and identifies patients who should be screened

“By sharing, you advance the science quickest.”

—Tomi Pastinen



“The systems become smarter with the more information they learn.”

—Marius George Linguraru



for a possible underlying genetic condition. A genetic counselor then reviews those records and healthcare providers are notified. Once identified, it works with the hospital system to educate physicians and patients on what the condition is, how to test for it, treat it, and manage it. The company was named co-winner of this year's \$150,000 Horizon Prize, a global innovation challenge focused on speeding diagnosis for people with rare disease. It's currently raising a series A venture round.

Separately, a joint venture between the AI-driven biomarker discovery company Scaillyte and the AI and applied data science company Volv Global is developing a rare disease diagnostic platform to identify rare diseases. Through the joint venture, Volv Global will identify potential patients with rare or difficult to diagnose diseases, who can then be enrolled in molecular biomarker discovery studies Scaillyte will lead.

Early detection of genetic diseases can play a critical role in improving outcomes for patients with these conditions, and if nothing else, avoid an extended diagnostic odyssey. In July, a study in *The Lancet Digital Health* found that deep learning technology to rapidly screen patients could accelerate the diagnosis of genetic diseases. Researchers at Children's National Hospital reported in a study of 2,800 pediatric patients from 28 countries that technology, which examined facial features, could detect disease patterns not obvious to the human eye. The technology can be easily used by physicians not trained in genetics or in countries with limited access to genetic testing to identify patients suspected of having a genetic condition.

A Children's National team led by Marius George Linguraru, principal investigators in the precision medical imaging laboratory of the Sheikh Zayed Institute for Pediatric Surgical Innovation, and Marshall Summar, director of the Children's National Rare Disease Institute, developed the technology. It uses artificial intelligence and machine learning to analyze biometric data and identify facial markers that are indicative of genetic disorders. They said the technology can provide with 90 percent ac-

curacy, early diagnosis of 128 genetic diseases across pediatric subjects in 28 countries.

Children's National in July 2020 entered into a licensing agreement with MGeneRx, a spinoff from the life sciences technology operating company BreakThrough BioAssets, to commercialize the pediatric medical device technology using biometric analysis software it had developed to screen photos for dysmorphic genetic diseases. The expectations are that as it processes more and more images, it will be able to detect a much larger group of genetic diseases that involve some form of facial dysmorphia.

“The systems become smarter with the more information they learn. So at least theoretically, the more it learns, the better we'll identify conditions. So, there should not be a cap. There should be more and more and more,” said Children's National's Linguraru. “The expectation that our technology has is that there is at least some facial dysmorphology.”

FDNA, which developed the Face2Gene product, an AI-based phenotyping technology that uses facial recognition analysis of images, said its technology is used by 70 percent of the world's geneticists today. In April 2021, the company launched an online genetic counseling service to improve access to genetic counseling. It said barriers to getting genetic counseling—including availability, cost, and awareness—can play a role in the long delays rare disease patients face in getting a diagnosis. The company said its FDNA Telehealth platform is designed to connect rare disease patients to a global network of genetic experts almost immediately.

But if AI is playing a critical role in providing a diagnosis of rare diseases, it is also being harnessed to address the related problem of a shortage of genetic counselors. One of the consequences of the proliferation of genetic sequencing has been a shortage of genetic counselors. It's left existing counselors to manage a heavy load as it has increased the demands of onboarding patients, consenting them, educating them, and interpreting results. The digital health company Igenify is helping providers and genetic counselors scale their services with its AI-

based platform that extends through the entire genetic testing process. Its system automates the translation of genetic data into actionable lab reports, and it is intended to allow a genetic counselor to manage a much larger load of patients by automating the process and using its platform to provide educational information directly to patients through an application.

“We want the computer to do exactly what a genetic counselor would want it to do, which means to ask the questions that the genetic counselor would want it to ask and nothing more, interpret it the exact way that the genetic counselor wants to interpret it, and then return the results and the recommendation exactly like a genetic counselor would want it to do,” said Doron Behar, founder and CEO of Igenity. “For example, we don’t want an AI machine to kick in and decide that a certain variant is not pathogenic anymore or is pathogenic suddenly. We want it all to be very supervised. We are not trying to invent the genetic counseling process from the start. We are trying to augment the genetic counselor and to allow them to supervise a hundred times more patients.”

Diagnosing Genetic Disease Prior to Birth

While many efforts have focused on shortening the diagnostic odyssey, new diagnostic technology has the potential to eliminate it completely by making the detection of rare disease possible before birth. While the ability to detect cell free DNA in the blood has given rise to liquid biopsies to detect DNA shed by tumors, the same basic approach has given rise to the detection of genetic disease by searching for fetal DNA in the blood of pregnant women. The so-called non-invasive prenatal testing (NIPT) is being used to detect a group of genetic diseases.

In fact, there has been a move to broaden the test from women who are considered at an elevated risk of giving birth to a child with a genetic disorder. In 2020, the American College of Obstetricians and Gynecologists updated its clinical practice guidelines to recommend the use of NIPT for all pregnant women, regardless

of age. Following the issuance of those recommendations, a number of payers updated their coverage policies to match these guidelines, but other payer policies on NIPT have limited its use to high-risk populations, even though it is considered to be a more accurate pre-natal screening method than conventional approaches, such as ultrasound or serum biochemical screening.

A study published in the journal *Ultrasound in Obstetrics & Gynecology* that looked at more than 2,200 women who received a non-invasive prenatal test result for a panel targeting 25 clinically significant single gene disorders found that 125 (5.7 percent) tested positive for one of the conditions. Women with ultrasound abnormalities or with a family history of one of the disorders covered by the test had a significantly higher positive rate. No false positive or false negative cases were reported.⁶

In March 2021, the sequencing giant Illumina, researchers at the University of Colorado, and the 3-million-member nonprofit HMO Harvard Pilgrim Health Care reported study results evaluating the impact of a risk-sharing agreement that opened insurance coverage of (NIPT) for pregnant women under the age of 35. The study, published in the journal *PharmacoEconomics*, found that thousands of women gained access to NIPT and that the economic impact was less than 3 cents per member per month.⁷ By expanding NIPT coverage to women under 35, it increased NIPT usage with only a modest increase in prenatal screening costs. They said that suggests patients and physicians may prefer a more accurate screening method. ■



Development

A Move from Patients to Funders to Collaborators



“We needed to be frugal with time. It was much better to have three parallel approaches even though you knew you could only move forward with one into the clinic. You don’t want to waste time having sequential failures.”

— Karen Chen, CEO, The SMA Foundation

In the annals of gene therapy, Jean Bennett holds a unique position. A professor of ophthalmology at the Perelman School of Medicine, Bennett’s work led to the development of Luxturna, the first gene therapy approved in the United States. Spark Therapeutics, which she co-founded, won approval for Luxturna in 2017 to treat patients with a specific mutation causing Leber congenital amaurosis, a rare retinal degenerative disease that is the leading cause of inherited blindness. Roche acquired Spark for \$4.8 billion in 2019.

With that pedigree, it shouldn’t have been surprising to see Bennett become one of the scientific co-founders of Opus Genetics, a company focused on developing gene therapies for inherited retinal diseases. Opus licensed its two lead assets from Bennett’s lab. The first, OPGx-001, is for pediatric patients with Leber congenital amaurosis caused by mutations in the LCA5 gene. The condition affects just one in 1.7 million people. Opus expects to enter human clinical trials in mid-2022. The company’s



Jean Bennett

second program, OPGx-002, is designed to restore protein expression and halt progression of vision loss due to retinal dystrophy caused by mutations in the RDH12 gene, which causes a different form of Leber congenital amaurosis, known as LCA13, which affects one in 288,000 people.

What made Opus Genetics unusual is that it was spun out of the Retinal Degeneration Fund, a venture philanthropy fund established in 2018 by the patient advocacy organization Foundation for Fighting Blindness. The foundation created the fund to drive research toward preventions, treatments, and cures for the entire spectrum of blinding retinal diseases. The patient organization’s CEO Ben Yerxa, who also heads the RD Fund, has a Ph.D. in organic chemistry and has previously worked in drug development inside biopharmaceutical companies. He is also acting CEO of Opus Genetics. The effort reflects a progression within patient advocacy to not just fund research, but to move upstream in the drug development process and into company creation to develop needed therapies for patients.



Ben Yerxa



“There were a number of gene therapies that we have been following, some that we funded, that were not getting picked up by mainstream VCs or some of the biotechs for licensing. We just got frustrated by the pace of that translation into the clinic, so we decided to set up a company that had a compelling business model to bring in a handful of these mostly smaller population gene therapies and get them into the clinic and developed for patients,” said Yerxa. “The way to make it happen was for us to lead the investment. We did the diligence. We brought the other syndicate funders into the deal and did all the heavy lifting.”

The RD Fund led the \$19 million Opus Genetics seed round, which included participation from the Manning Family Foundation and Bios Partners. With the financing, the RD Fund’s initial \$73 million became fully invested. Opus was the final of ten investments made by the RD Fund’s first fund. The fund targets investments of \$2 million to \$5 million in companies with therapies that are 18 to 24 months from entering the clinic. The RD Fund is now raising a new fund in part with returns it’s already seen. In 2020, Novartis acquired the optogenetics therapy developer Vedere Bio for up to \$280 million. The RD Fund was an investor in Vedere.

Organizations like the Cystic Fibrosis Foundation blazed trails with its venture philanthropy funding of Vertex Pharmaceuticals that resulted in groundbreaking therapies that have changed the outlook for many patients with cystic fibrosis. Other organizations, such as the Multiple Myeloma Research Foundation and the Myelin Repair Foundation, have helped change the way researchers and drug developers interact with patient organizations and showed that they could be not just funders, but collaborators. And while there have been a number of parents of children with rare diseases who have been moved to launch rare disease drug development companies (Brad Margus and John Crowley, board members of Global Genes, are among the most prominent examples), patient organizations are becoming increasingly sophisticated about the drug development process, what it takes to bring pharmaceutical companies to the table, and tapping greater amounts of capital to ensure promising therapies advance beyond the translational science gulf and make it into the clinic.

A growing number of patient organizations are playing a more direct role in the drug development process by extending their funding beyond basic academic research, and in the process often capitalizing on the know-how and

A Rare Disease Patient Foundation That Was an Innovative Funder Innovates Again

The Cystic Fibrosis Foundation, a pioneer of the venture philanthropy model to fund rare disease drug development, broke new ground in 2021 with a first-of-its-kind strategic partnership with a venture capital firm.

The foundation, which has provided venture funding to a number of drug developers, in 2014 sold its rights for CF treatments developed by Vertex for \$3.3 billion, which has provided it with an impressive war chest.

In November 2021, the foundation entered into a strategic partnership with the venture capital firm Flagship Pioneering to develop therapeutics that address the unmet needs of people living with cystic fibrosis by leveraging the innovations and teams of multiple Flagship-founded companies.

Through the agreement, the Cystic Fibrosis Foundation has committed up to \$110 million to Pioneering Medicines to bring forward multiple development candidates and develop these candidates to human proof of concept. Pioneering Medicines is a strategic initiative within Flagship Pioneering that is dedicated to conceiving and developing a broad portfolio of life-changing treatments by leveraging and expanding the use of Flagship's innovations.

Pioneering Medicines is bringing together an integrated team to develop life-changing treatments and deliver benefits to patients much sooner than any company could independently deliver. Pioneering Medicines and the Cystic Fibrosis Foundation will

partner with multiple companies within the Flagship ecosystem, leveraging emerging technologies including Tessera Therapeutics' Gene Writing technology, targeted delivery modalities, and

mally thick, sticky mucus that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death. The median age of death is in the early 30s.



“We have an unparalleled opportunity to create innovative products that combine platform technologies to help address the unmet needs of the cystic fibrosis community.”

—Noubar Afeyan

RNA technologies. The teams will work together to harness their unique technologies and develop individual asset companies specifically focused on potential treatments for cystic fibrosis.

Cystic fibrosis (CF) is a rare, life-shortening genetic disease. It is caused by mutations in the CFTR gene that lead to a defective or missing cystic fibrosis transmembrane conductance regulator (CFTR) protein. Children must inherit two defective CFTR genes—one from each parent—to have CF. There are approximately 2,000 known mutations in the CFTR gene. The defective function or absence of CFTR protein results in poor flow of salt and water into and out of the cell in a number of organs. In the lungs, this leads to the buildup of abnor-

Despite recent advances, approximately 10 percent of individuals living with cystic fibrosis have rare or nonsense mutations and do not have any effective treatment options.

“There is a tremendous opportunity to expand the impact of Flagship's innovative bioplatforms by creating medicines in disease areas beyond where the individual companies are initially focused,” said Noubar Afeyan, founder and CEO of Flagship Pioneering. “Through Pioneering Medicines and our new collaboration with the Cystic Fibrosis Foundation, we have an unparalleled opportunity to create innovative products that combine platform technologies to help address the unmet needs of the cystic fibrosis community.”



experience of industry veterans in their own ranks to forge collaborations with industry, or, as with Opus Genetics, directly create their own companies to conduct the drug development needed to address their patients' needs.

"We're finding that there are a lot of science and programs that are in this translational moment where they either need to be, or they're actively spinning out of academia into biotech and they still need our help," said Foundation for Fighting Blindness' Yerxa. "For us to follow the science and the programs as they're being brought into biotech for that first clinical translation, we find that having us at the table, and writing a check to have influence at the table, is the best way to ensure the probability of success."

Evolving with Success

Loren Eng and Dinakar Singh founded the SMA Foundation in 2003 after their daughter Arya was diagnosed with the progressive neuromuscular condition spinal muscular atrophy. The organization today is among the most successful examples of patient organizations influencing the development of drugs for the rare diseases on which they focus. The company's partnership with PTC Therapeutics and Roche to discover and develop Evrysdi, the first and only treatment for the condition that can be taken at home, shows how patient organizations can be true collaborators who are actively involved in the ongoing development of a therapy. But they also show how the pursuit of therapies by these organizations can evolve, as treatments come to market that address certain needs but leave others to be addressed.

In March 2021, the SMA Foundation and PTC Therapeutics entered into a collaboration focused on regenerative medicine to further advance scientific research and development of new treatments for SMA and other neuromuscular disorders. The partnership will provide funding of up to \$60 million to academic institutions and other collaborators to advance foundational research in regenerative medicine. The funding will come in part from royalties paid to the SMA Foundation from Evrysdi sales.

Spinal muscular atrophy (SMA) is caused by defects in the survival motor neuron 1 (SMN1) gene that encodes the SMN protein. The SMN protein is critical to the health and survival of motor neurons, the nerve cells in the spinal cord that are responsible for muscle contraction. There are different forms of SMA. SMA type 1 is the most severe form and generally results in death before age two. Patients with milder forms of SMA may not have symptoms of muscle weakness until later in childhood or even adulthood.

Even though the SMA community saw three significant therapies approved for the condition thanks in part to the groundwork the foundation had laid for research into the condition—the antisense oligonucleotide Spinraza at the end of 2016, the gene therapy Zolgensma in 2019, and Evrysdi in 2020—the foundation saw the need for additional therapies. "In neuromuscular disease, correcting the underlying cause is just the first step," said Eng, president and co-founder of the SMA Foundation, when the foundation announced the new partnership with PTC Therapeutics. "Patients need therapies to help restore lost function."

One thing that has allowed the SMA Foundation to engage effectively with industry is the expertise it has in house. Karen Chen, who joined the SMA Foundation as its CEO in 2007, earned a Ph.D. in neuroscience from the University of California, San Diego and had experience working for biopharmaceutical companies. She had been a post-doctoral fellow at Genentech, a director at Elan and later at Roche, and a co-founder and CEO of Imago Pharmaceuticals. The foundation initially spent a lot of time knocking on the doors of biopharmaceutical companies trying to get them interested in pursuing therapies for SMA. Even though the foundation had a seasoned board with members from industry and staff who also came from industry that could provide introductions, there was little interest at the time.

"We had very little luck trying to convince them, especially Big Pharma, to have a program in a rare disease," she said. "That's certainly changed. It's not so hard now. Part of it is due to the success of SMA drugs, but 20 years ago it was quite challenging."

"Patients need therapies to help restore lost function."

—Loren Eng



“We knew Arya. We knew the family. They were highly focused. We were highly focused. So, we pushed hard.”

—Stuart Peltz



The foundation made several early investments to remove barriers to drug companies pursuing therapies. This included some obvious steps, such as conducting a long and extensive natural history study, investing in animal models and cell models, and collecting biological samples. But the foundation also took other steps to do more preclinical testing that would meet the standards that potential industry partners would do themselves. “Because we knew that these were issues that existed in trying to sell a program to pharma, we adopted those practices in house. So, when we actually did speak to pharma and biotech, we were able to show we did this study at CROs that you yourself use. This is the protocol. It’s all very reproducible. And that was the same with *in vitro* models.”

To help convince industry partners to collaborate with them, the foundation worked with clinicians to develop well-established endpoints for clinical trials. The foundation viewed its core mission as accelerating the development of treatments for SMA and one way it saw to do that was to fund studies to develop standards of care. The thinking was that doing so would ensure that whether a company conducted a clinical study in San Francisco, Dubai, or Brussels, the population of patients it drew from would have a similar standard of care. That would avoid wide discrepancies in such endpoint measures as survival.

When the organization began working with PTC Therapeutics, the company was already working in rare neuromuscular conditions. It was pursuing a potential therapy for Duchenne muscular dystrophy. In 2005, when PTC was a development stage company, the SMA Foundation first approached it to develop therapies for SMA. The following year, the two announced a research and development collaboration designed to leverage PTC’s platform for gene expression modulation technology to identify and develop new small molecule therapeutics for use in the treatment or prevention of SMA.

Though Chen’s drug development expertise has proved valuable to the collaboration, the initial work with PTC began prior to Chen joining the foundation. Stuart Peltz, CEO of PTC Therapeu-

tics, said the foundation provided a combination of financing, SMA expertise, and motivation that drove the work—getting to know the condition in a personal way by getting to know the SMA Foundation’s Eng and her daughter Arya.

“They had the financial wherewithal to be able to be focused on trying to get a drug for their kid. It isn’t just a professional CEO in a patient advocacy group talking,” he said. “It was a mom with a kid who really wanted that drug. Anyone who cares at all, there’s that extra umph. We knew Arya. We knew the family. They were highly focused. We were highly focused. So, we pushed hard.”

Chen said one difference she found working for the foundation rather than industry was a change in attitude on spending. She said when she worked in industry, she felt the need to be frugal, but the foundation was more aggressive about making investments in preclinical programs, pursuing multiple programs at once.

“At the foundation, the first thing I found surprising and eye-opening was that it was okay to spend lots of money,” said Chen. “We needed to be frugal with time. It was much better to have three parallel approaches even though you knew you could only move forward with one into the clinic. You don’t want to waste time having sequential failures.”

In 2011, Roche, PTC Therapeutics, and the SMA Foundation entered into a licensing agreement for PTC’s Spinal Muscular Atrophy program developed in collaboration with the SMA Foundation. Roche paid PTC \$30 million up front and up to \$460 million in potential milestone payments, as well as double digit royalties. But the most remarkable aspect of the agreement is that it created a joint steering committee comprised of members from Roche, PTC, and the SMA Foundation in which the three members had an equal say in decisions about the development of what would become Evrysdi.

Paulo Fortuna, global head and senior vice president of Neuroscience, Immunology, Ophthalmology, Infectious, and Rare Diseases at Roche, said he could not think of another example where drug developers not only gave a

patient organization a seat at the table in a development program, but one where they had an equal vote.

The foundation's insights and relationships proved valuable, as well as its ability to provide an additional perspective. It could offer insights on clinical trial endpoints based on an understanding of what matters to patients and their families. It had global relationships with investigators and clinical research sites. And when the industry partners had disagreements on certain issues, it was seen as a neutral third party that could cast a deciding vote and diffuse conflicts and keep the project moving.

Industrializing Patient-Led Discovery

While the SMA Foundation's most recent collaboration with PTC to fund academic research provides a built-in pathway to advance promising discoveries from the lab to the market, a separate effort between a patient organization, an academic researcher, and a gene therapy developer is providing a broader platform for rare disease organizations seeking to develop gene therapies for their conditions.

Lori Sames' daughter Hannah was four years old when she was diagnosed in 2008 with giant axonal neuropathy (GAN), a rare inherited genetic disorder that affects both the central and peripheral nervous systems and is caused by loss-of-function mutations in the gene coding for



Paolo Fortuna

the protein gigaxonin. Many children with GAN show symptoms and features before the age of five, including progressive scoliosis, contractures, atrophy of the spinal cord, giant axons—also known as nerve fibers—and abnormalities of the white matter in the brain. Currently, there are no approved treatments for GAN, which often results in death for patients in their late teens or early twenties.

Doctors offered Sames a grim prognosis. They said that the number of patients with GAN was too small for a drug company to invest in developing a gene therapy. Sames at first spent 20 hours a week searching the Internet for researchers working on the disease and she could only find one. She and her husband decided to raise money and fund research. They launched Hannah's Hope Fund, a nonprofit focused on funding research into GAN and the development of therapies.

When she read about patients being dosed with an experimental gene therapy developed by gene therapy pioneer Jude Samulski at the University of North Carolina at Chapel Hill, she reached out to him. Hannah's Hope Fund had just organized a scientific meeting about GAN and after talking to Sames, Samulski sent a young researcher named Steven Gray to attend the meeting. Shortly after meeting him at the conference, the nonprofit began funding his work and three years and three months later, they were sitting down with the FDA to discuss an application to begin human clinical trials.

To get to that point, Hannah's Hope Fund raised more than \$6 million through 5K runs, golf tournaments, galas, and anything else they could think of to raise money. They twice won Pepsi Refresh Challenge grants of \$250,000 each. When they didn't have the funds to conduct a clinical trial, they turned to the National Institutes of Health.

Investigators dosed the first patient in the clinical trial in 2015 and Hannah became the fifth patient to be dosed in the study in 2016. Sames said today, Hannah's condition is stable, but she did pay a price for the delays

“Those delays that year pretty much robbed her of a much longer life.”

—Lori Sames



Lori and Hannah Sames

in getting treated and believes if they had the funding to do the trial themselves it would have accelerated the process.

“She was pretty fragile. We felt such urgency. Her motor function measures scores in the year before her injection were cut in half, but those 12 months were critical in terms of disease progression for Hannah’s long-term future. Those delays that year pretty much robbed her of a much longer life.”

The work of Hannah’s Hope Fund with Gray, though, stands to benefit many more patients than those with GAN. The work done to create a gene therapy for GAN has been replicated by Gray and his lab, which is now at the University of Texas Southwestern in Dallas. By using the same vector, the same intrathecal form of delivery, and the same manufacturing process, Gray has developed a platform that he is using to advance gene therapies for other rare, genetic conditions involving the central nervous system. And, through a novel partnership with Taysha Gene Therapies, there is now a translational mechanism in place to advance these therapies from the lab to the market.

A Transformational Partnership

UT Southwestern’s Gray had been bootstrapping the work, writing grants, and having patient groups raise money. In the summer of 2019, he sat down with R.A. Session II, the former senior vice president of corporate strategy and business development for AveXis, which developed the first FDA approved commercial gene replacement therapy Zolgensma. Session, who had been born and raised in Dallas, was taking time off following Novartis’ acquisition of AveXis. Through his work at AveXis, he knew Gray, and met with him to learn about his work at UT Southwestern.

When Gray showed Session a slide of about 30 preclinical programs, Session was surprised. “This is a company, not an academic research lab,” Session told Gray. “How are you planning on taking on all of these?” Session told him there

was plenty of money being invested into gene therapy. It was a hot area. He needed to form a company to fund the work necessary to move these therapies from the lab to the patient.

“If you spun this out into a company,” Session told him, “You’d never have to fundraise again.”

Gray asked Session if he would help him spin out a company and be its CEO. Though he was reticent at first, as Session got closer to the technology, the indications Gray was pursuing, and met patients, he decided to take on the work full-time. From his kitchen table, in the midst of the COVID-19 pandemic, Session was able to quickly raise \$30 million in initial capital starting with his former AveXis CEO Sean Nolan, who was investing his own family money, and Paul Manning of PBM Capital, the first investors in AveXis. In a short amount of time Session raised a total of more than \$300 million, which included a \$95 million series B round in August of 2020 and a \$181 million initial public offering one month later.

Taysha formed an unusual strategic collaboration with the UT Southwestern Gene Therapy Program to move its AAV gene therapies from the lab to the market. Gray, director of the Viral Vector Core and assistant professor in the Department of Pediatrics, and Berge Minassian, division chief of Child Neurology, serve as chief advisors to the company. Under the partnership, UT Southwestern conducts discovery and preclinical research, lead IND-enabling studies, provides clinical GMP manufacturing, as well as executing natural history studies. Taysha leads all clinical development, regulatory strategy, commercial manufacturing, and commercialization activities. A joint steering committee, composed of key leadership members from Taysha and UT Southwestern, governs the collaboration.

The company also acquired exclusive worldwide rights to the GAN gene therapy from Hannah’s Hope Fund for an upfront payment of \$5.5 million. The organization will be eligible to receive clinical, regulatory, and commercial milestones totaling up to \$19.3 million, as well as a low, single-digit royalty on net sales upon commercialization of the product.

“If the biology is clear and we have the technology to address it, it really allows us to go after those Ns of hundreds versus having some arbitrary cutoff.”

—R.A. Session II





Will Woleben



The Woleben family

Built for Speed

As a reflection of how this approach has changed the speed of moving from a disease to a gene therapy that's ready to move into the clinic, consider Gray's work to develop a gene therapy for SURF1 Leigh syndrome, a rare neurometabolic disorder. SURF1 causes progressive degeneration of the central nervous system. It is considered a mitochondrial disease because it affects the ability of the mitochondria, known as the powerhouse of the body's cells, to convert food and oxygen into energy. The condition affects development of mobility, posture, and mental capacities in children.

In 2014, doctors diagnosed Kasey Woleben's 2-year-old son Will with SURF1. When she and her husband asked about treatments, they were told gene therapies were too far out of reach. Instead of wasting their time and money pursuing one, they should take their son home and enjoy what time they had left with him.

"The outlook is not good, but with SURF1 children, it's almost like ALS because these

children have their cognitive minds. They know exactly what's going on. They're just losing their abilities," said Woleben, whose son is now 10. "My son is no longer able to walk, to talk, or eat, but cognitively he knows exactly what's going on. He's super smart. These kids usually pass away from respiratory distress, respiratory illness like a virus. It's usually pretty quickly once an infection sets in."

The couple, who live in the Dallas suburb of McKinney, Texas, started searching the world for potential experimental therapies when they had a chance meeting in 2018 with Berge Minassian, a pediatric neurologist in their own backyard who at the time was recruiting Gray from UNC Chapel Hill.

The Wolebens met with Minassian, Gray, and others at UT Southwestern and brought a binder with their son's complete medical history and MRI studies, as well as all the published research they had gathered on SURF1 and told them they thought it would be a good candidate for a gene replacement therapy. After some preliminary research, the researchers

agreed SURF1 would be a good candidate, but they offered them some caveats. They would need to raise millions of dollars to fund the preclinical work. And while they are raising all that money, they should realize that it may not work. If it proved promising and advanced to human clinical trials, there was no assurance their son would be enrolled in a clinical trial. He would need to apply like anyone else and might not be selected.



“These children have their cognitive minds. They know exactly what’s going on. They’re just losing their abilities.”

—Kasey Woleben

With that, the Wolebens co-founded the SURF1 Foundation along with other families with children with the condition. It was later renamed the Cure Mito Foundation to reflect a broader mission around mitochondrial diseases. Through golf tournaments, lemonade stands, Facebook fundraisers, and any other way they could think of, the organization raised \$1 million in nine months.

Today the preclinical work is approaching completion. Ultimately, the organization raised about \$1.5 million when Taysha Gene Therapies stepped in and took over development. That spared Cure Mito the need to raise an additional \$1.5 million for preclinical studies. As Woleben’s son Will turned 10 in December, the company was readying to file an application with the FDA to begin clinical testing of the gene therapy.

In the meantime, Cure Mito is working on a patient registry with AllStripes for SURF1 Leigh syndrome and a general Leigh syndrome registry with AllStripes and Sanford Research’s patient registry platform CoRDS. Taysha is also funding a natural history study with the expectation that it will use that as a control arm for a pivotal study of the therapy.

The movement from the conception of a gene therapy to being on the cusp of filing an application with regulators to begin clinical trials moved with impressive speed for SURF1. In part, that was because of a belief that time was more precious than money. The organization decided to take the financial risk of moving in parallel on several projects

at once rather than waiting to see if the gene therapy showed early signs of promise.

“We worked in parallel doing toxicology studies, doing mouse model studies, everything in parallel knowing that we’re funding these projects and at any time it could fall through and we’re out half a million dollars. But to us that didn’t matter because nothing was being done for this disease,” said Woleben. “It was a chance that we needed to take. If the toxicology study comes back terrible, then you basically have to stop everything and you’re out whatever money. But to us, that didn’t mean anything.”

The other good fortune that the Cure Mito Foundation had was that after it began working with the Steven Gray Lab at UT Southwestern, Taysha Gene Therapies, a company built around a partnership with the gene therapy program at UT Southwestern, essentially put into place a translational pathway for work performed at Gray’s Lab to move into clinical trials and eventually commercialization.

Removing Barriers

At the start of 2021, Taysha and UT Southwestern launched what they dubbed a new innovation fund, which expanded the relationship. The fund provides a way to accelerate the work between the two partners by eliminating the need to negotiate and write new agreements between the partners anytime a new gene therapy target is identified and pursued.

“We wanted to have a pool of money that was already approved by Taysha and the university to be able to pull from to quickly initiate new research,” said Session. “This is a cross-functional fund that is managed by both our Taysha R&D leadership and the R&D leadership at UT Southwestern Gene Therapy Group. They collectively approve new ideas, new targets, new assays, or experiments to go after.”

Today, Taysha has about 180 employees, but it also has the benefit of UT Southwestern’s Gene Therapy Group, which effectively boosts its headcount to 250 FTEs. Taysha’s pipeline, which consisted of 15 programs at launch, is now nearly twice that with 26 programs, five of which were expected to be in the clinic by the end of 2021. The most advanced of those programs, the GAN gene therapy, is entering a pivotal study and could be approved as early as 2023.

Taysha’s Session notes that a number of patient organizations have been instrumental in starting and advancing various gene therapy programs, pointing to organizations like Hannah’s Hope for the GAN program, Taylor’s Tale for CLN1 Disease, and the Cure Mito Foundation for SURF1. But the compelling aspect of the work from Gray that has made the various CNS conditions viable for a commercial biotech to pursue is that all of the work is leveraging the same AAV9 vector, the same form of intrathecal delivery, and the same cell culture to produce the vector across all of the CNS conditions being pursued.

“It allows us to be able to go after smaller indications that from an economic perspective, you would say wouldn’t necessarily get the return on investment. For us, if the biology is clear and we have the technology to address it, it really allows us to go after those Ns of hundreds versus having some arbitrary cutoff,” said Session. “It’s another reason why we’re able to do so much and do it at scale, and the speed in which we’re able to do it.”

For Want of a Nail

While the alliances between patient organizations, Gray’s lab, and Taysha have provided a promising and relatively fast pathway to develop gene therapies for rare CNS disorders, it largely remains incumbent on a small group of patients to find the money needed to advance through the earliest part of the process. For some groups, that can represent a significant barrier that results in delays in bringing treatment to patients.

Amber Olsen, founder and executive director of United MSD Foundation, began working with Gray in 2017 to develop a gene therapy for multiple sulfatase deficiency (MSD) a rare, genetic disease that causes a buildup of natural cellular waste throughout the body and leads to premature death usually before age 10. The condition has been likened to Alzheimer’s disease in a child.

Doctors diagnosed her daughter Willow with the condition in 2016 at the age of 2 after she began to stumble when she walked. The condition progressed rapidly after the diagnosis as she declined rapidly. By the end of the year, she stopped walking and was placed on a feeding tube. Olsen quickly found researchers working on the condition and



“I’m having a hard time raising \$300,000. I don’t know how I’m going to raise \$3 million.”

—Amber Olsen





Amber and Willow Olsen



was eventually pointed to Gray, who was then at UNC Chapel Hill. At the time, the group expected it would need to raise \$3 million to fund preclinical work and could be in the clinic in 18 months.

There are less than 100 known cases of MSD globally, although that is expected to increase with improved diagnosis and greater use of genetic testing. Gray developed a gene therapy for the condition and the organization funded the testing of the therapy in a mouse model at The Jackson Laboratory, which produced promising results, but since then they've been unable to raise enough money to fund the next studies that are needed.

"We tried to raise some money and we still continue to try. I'm having a hard time raising \$300,000. I don't know how I'm going to raise \$3 million. We got on Good Morning America. We had a Huffington Post article. We had some shots," said Olsen. "We didn't have any kids that were famous and unfortunately I'm not in a circle of people that have a ton of money.

People are generous and they got us very far along, but you've got to raise millions."

Olsen hasn't given up. To remove barriers to getting commercial interest in the therapy, the organization is using what resources it has to put into place elements that would allow a biotech company to step in and take over development. It already had scientists create a retrospective natural history study and it is funding a prospective natural history study that a pharmaceutical company would normally do. It's also created a biobank, patient registry, and is planning a patient-centered outcomes survey. Olsen is hoping Taysha will pick up the gene therapy and complete the preclinical work on it with those other pieces in place.

While she is working to see the therapy advance into clinical trials, she doesn't expect her daughter, who is 8, to be selected for any study because her condition has progressed significantly.

"Seeing my daughter every day is tough but having to talk with new families and watching

their children decline over and over and over again is also heartbreaking. A year-and-a-half ago, we had a new family that if we had this going right now, their child could be treated and saved. That's difficult as well," she said. "We've seen children die. We have had six new diagnoses this year and I can't wait to be able to say, 'Hey, there's a clinical trial. Go here.'"

Leveraging Resources

Though raising money remains a barrier for foundations, even those with relatively limited resources are finding that they can catalyze drug development by making smart investments. Consider the CMT Research Foundation, which is focused on driving therapeutic development for treatments and cures of Charcot-Marie-Tooth disease, a rare disease that causes peripheral nerve degradation. The condition can be caused by mutations to more than 100 genes, each with potentially multiple different mutations. Though there are several types of CMTA, the most common form is CMT1A, which results in progressive nerve degradation, progressive muscle atrophy in the legs and arms, and leads to problems with walking, running, balance, and manual dexterity.

The approach the CMT Research Foundation has taken has been to understand the barriers to drug development for CMT and to find ways to address those. For instance, one challenge of using gene therapies is delivering therapies to the peripheral nervous system. To address that, the foundation reached out to James Dahlman, an associate professor in the Department of Biomedical Engineering at Georgia Institute of Technology and Emory School of Medicine, who focuses on targeted delivery of genetic medicines. The organization in February launched a research collaboration with Dahlman to develop lipid nanoparticles to deliver therapies to the Schwann cells of the peripheral nervous system to treat CMT. Schwann cells are specialized cells that protect the peripheral nerves and whose dysfunction causes disease in the most common forms of CMT. "We designed a project, we provided funding, and we started that with Dr. Dahlman,"

said CMT Foundation's Susan Ruediger. "It's knowing exactly what our barrier is and finding all of the people who can work on that."

In June 2020, the CMT Research Foundation funded a project to screen drug candidates for CMT4B1, a severe and debilitating form of CMT. Under a three-way collaboration, CMT is funding the effort by the Human Inherited Neuropathies Unit at the Ospedale San Raffaele in Milan, Italy to screen compounds developed by AcuraStem in CMT4B1 models developed by Alessandra Bolino at the institute using patient derived stem cells. AcuraStem had been working on extending the survival rate of motor neurons and Ruediger said it was not familiar with CMT when the research foundation approached it. The foundation suggested the work it was doing had relevance in CMT and funded the screening project.

The organization has also provided seed funding to key partners that have allowed them to leverage that to raise additional money to advance work in CMT. When the organization came across DTx Pharma at a BIO International Convention, discussions led, in January 2019, to \$125,000 to fund a project to screen a library of RNA-based compounds that could down regulate PMP22, a protein that is over-produced in CMT. DTx has platform technology that allows it to deliver these therapies to the peripheral nervous system. The funding from the CMT Research Foundation helped the company secure a \$350,000 National Institutes of Health grant to continue the project and that was followed by a \$100 million venture financing the following year in which CMT1A is one of two lead programs the company was pursuing.

"They would never have started a CMT program if we hadn't introduced the disease to them and given them the seed funding. And because of that seed funding, their data was so good, because their technology was so well suited for CMT, that they were able to raise a hundred million plus," said Ruediger. "Now their commitment is to take their drug all the way through to clinical trials. That's what we do. We're catalytic funding." ■

"Now their commitment is to take their drug all the way through to clinical trials. That's what we do. We're catalytic funding."

—Susan Ruediger



Seeking Gains as New Threats Emerge



“We should be concerned whether those who purport to be consumer advocates are actually going to harm patients.”

—James Valentine, an associate with Hyman, Phelps & McNamara

The most consequential regulatory decision from the U.S. Food and Drug Administration in 2021 for the rare disease world may have been its decision to grant approval to a treatment for one of the most common causes of death in the United States. That’s because when the agency approved Biogen’s monoclonal antibody Aduhelm under its accelerated approval mechanism, it placed the agency in a firestorm as critics charged the agency approved a costly drug without scientific evidence it would benefit patients with the condition. The outrage over the approval has put the FDA’s accelerated approval mechanism in the crosshairs of critics who want to reform the agency’s use of the program.

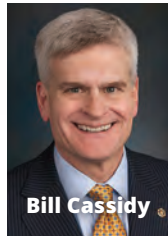
The Accelerated Approval program allows the FDA to approve therapies for serious medical conditions that fill an unmet medical need that demonstrates efficacy through the use of a surrogate endpoint that is believed to predict a clinical benefit even through it is not itself a measure of such. The use of a surrogate endpoint can greatly increase the speed with which a drug can win approval. But the sponsor still must conduct a post-marketing phase 4 study to demonstrate the drug actually provides a clinical benefit. If it fails in that study, the agency could pull the product from the market.

Aduhelm won accelerated approval in June 2021 despite 10 of the 11 members of the Peripheral and Central Nervous System Advisory Committee that reviewed drug voting that the agency should not approve it. One member voted “uncertain.”

Three of the advisory committee members resigned from the committee in the wake of the approval. “This might be the worst approval decision that the FDA has made that I can remember,” said Aaron Kesselheim, a professor of medicine at Harvard Medical School and Brigham and Women’s Hospital, who resigned over the approval after serving on the committee for six years.¹

In a letter to the members of the advisory committee, Billy Dunn, director of the Office of Neuroscience at the FDA’s Center for Drug and Evaluation and Research, offered the agency’s rationale for its decision. He noted that the accelerated approval pathway is for drugs that are expected to provide a meaningful advantage over available therapies to treat serious diseases, but where there is residual uncertainty regarding the drug’s ultimate clinical benefit. “To be approved under this pathway, there must be substantial evidence of the drug’s effectiveness on a surrogate endpoint—usually an endpoint that reflects the underlying

disease pathology (accelerated approval can also use an intermediate clinical endpoint),” Dunn wrote. “An effect on this surrogate endpoint must be shown to be reasonably likely to predict clinical benefit. We concluded that these requirements were met for [Aduhelm], with substantial evidence that the drug reduces amyloid beta plaque, and that this reduction is reasonably likely to predict clinical benefit.



called for a hearing because of the fiscal impact the decision could have. “This is a historic, watershed moment in the fight against Alzheimer’s disease, but approval of the new product has dramatic implications for our health care

system that stretch well beyond the scope of FDA’s jurisdiction. wrote Senators Bill Cassidy (D-Louisiana), and Elizabeth Warren, (D-Massachusetts). “We thus urge you to convene a hearing to examine the vexing new questions and challenges that approval raises for the Medicare program and other health programs within the Senate Finance Committee’s jurisdiction.”

The large number of patients with Alzheimer’s disease and the \$56,000 a year price tag for Aduhelm helped fuel harsh criticism of the FDA with charges that industry and patient organizations had “progressively lowered” the agency’s standard for approval. “The need for outside oversight is clear, given the continuing failure of the FDA to listen to its advisers, stand up to industry and consumer-group pressure and draw clear distinctions between drugs that work and drugs that only cause changes in lab tests of uncertain relevance,” Kesselheim and Jerry Avorn, a fellow professor of medicine at Harvard Medical School, wrote in an op-ed in June 2021 in *The New York Times*. “We cannot let this regulatory erosion send us back to a prethalidomide era.”²

The U.S. Department of Health and Human Services Office of the Inspector General in August 2021 announced it had launched a review of the FDA’s Accelerated Approval pathway. “The FDA’s approval of Aduhelm raised concerns due to alleged scientific disputes within the FDA, the advisory committee’s vote against approval, allegations of an inappropriately close relationship between the FDA and the industry, and the FDA’s use of the accelerated approval pathway,” the Office of the Inspector General said in announcing the review. The review will look at how the agency implements the accelerated approval pathway including a review of its interactions with outside parties, relevant policies and procedures and its compliance with them, and make appropriate findings and recommendations based on a sample of drugs approved using

Democrats in Congress followed suit. The House Committee on Oversight and Reform that same month announced it would launch an investigation into the FDA’s approval of Aduhelm. And Democrats in the Senate Finance Committee

Orphan Drugs Approved Under FDA Accelerated Approval

	Orphan Drugs Approved Under Accelerated Approval	All Drugs Approved Under Accelerated Approval	Total number of Orphan Drug Approvals	Percent of Orphan Drugs Approved under Accelerated Approval
2021	10	14	26	38%
2020	11	12	31	35%
2019	6	9	21	29%
2018	4	4	34	12%
2017	5	6	18	28%
2016	5	6	9	56%
2015	5	6	21	24%
Total	36	43	134	27%

Source: U.S. Food and Drug Administration

the accelerated approval pathway, which will include Aduhelm. A report is expected in 2023.

Many of the defenders of accelerated approval were voices in the rare disease community. Indeed, the mechanism has been essential for getting orphan drugs to market. A Global Genes analysis of FDA approvals under the program between 2015 and 2020 found that 84 percent of all drugs approved under the program had orphan designations. In all, some 27 percent of orphan drugs that won approval during that time did so through the accelerated approval pathway.

“We should be concerned whether those who purport to be consumer advocates are actually going to harm patients by shrinking what has, for example, totally changed the life expectancy and quality of life for people living with cancers,” said James Valentine, an associate with Hyman, Phelps & McNamara and an expert in regulatory law. “We should have that same tool available in rare diseases.”

While any alterations to the FDA’s application of the accelerated approval pathway could slow the approval of new therapies for rare diseases, the bigger concern rare disease advocates have is the potential impact of any such changes on the investment landscape for rare disease therapies. “Any moves that erect additional barriers to approvals will likely directly result in intensified reluctance to invest in future biomedical innovation,” wrote Barth Syndrome Foundation Executive Director Emily Milligan and the foundation’s Chair Katherine McCurdy in an opinion piece in *STAT*, “especially for ultra-rare diseases, and pose dire consequences for people living with the vast majority of the estimated 7,000 rare diseases for which there are currently no approved treatments.”³

No Love for Orphans

The attack on the accelerated approval pathway is not the only concern rare disease advocates are facing as other developments threatened to weaken incentives for rare disease drug development. Congress reduced the benefits of the Orphan Drug Tax Credit in

2017 when it passed the Tax Cut and Jobs Act. That legislation cut the total amount of the tax credit for qualifying clinical testing expenses from 50 percent to 25 percent. Lawmakers in 2021 sought to once again slash benefits the Orphan Drug Act conferred.

The Build Back Better Act, the Biden Administration’s ambitious plan to create jobs, cut taxes, and reduce expenses for working families is being offset by taxing large corporations and the wealthiest individuals. But among the offsets the plan includes to fund the programs it creates is an end to tax credits under the Orphan Drug Act for qualified clinical testing expenses for all but the first approved orphan use of a new drug. The EveryLife Foundation for Rare Diseases said the legislation would “fundamentally alter the rare disease pipeline” and discourage companies from pursuing the development of rare disease therapies.

“Our patient communities need more options, more hope, and more investment in rare disease research,” the EveryLife Foundation said. “The proposed change to the orphan drug tax credit will not result in any benefit to patients and stands to cause irreparable harm to the progress and innovation in rare disease therapeutic development.”

The 1983 Orphan Drug Act was passed to help incentivize investment in rare disease research and therapeutic development. Until its passage, there was little research being done and nearly no treatment options for those diagnosed with a rare disease. Over the last several decades, the Act has proven to be a great success, enabling life science companies to address a growing number of unmet needs for people living with rare diseases. Since implementation of the Orphan Drug Act in 1983, there have been more than 1,000 FDA approvals for rare disease treatments, with more than 25 percent of those approvals occurring in the last three years. The Orphan Drug Tax Credit, already diminished in 2017 under the Tax Cut and Jobs Act from 50 percent to 25 percent, remains a critical program for sustained innovation and investment for innovator companies that exclusively focus on life-changing development programs for treatments for rare diseases.

“We cannot let this regulatory erosion send us back to a prethalidomide era.”

—Jerry Avorn



FDA Readies for PDUFA Renewals

As the FDA prepares for renewal of the Prescription Drug User Fee Act (PDUFA), in September 2021 it outlined in the *Federal Register* a set of proposals it would recommend to Congress. The first PDUFA legislation passed in 1992 and the reauthorization is passed by Congress for periods of five years. The reauthorization of PDUFA the agency is working on will be the seventh incarnation of the legislation. The proposed recommendations to Congress for PDUFA reauthorization follow a series of discussions between the FDA, industry, and stakeholders started in September 2020. New legislation will be needed to allow the FDA to continue collecting prescription drug user fees in future fiscal years once the existing PDUFA expires in September 2022.

PDUFA authorizes the FDA to collect user fees from industry to support the review of applications for new drugs and biologics in a timely manner. As part of FDA's negotiations with industry during each reauthorization, the agency agrees to certain performance and procedural goals and other commitments that apply to aspects of the human drug review program. Congress passes the legislation for five-year periods at a time.

Several of the proposals the FDA is putting forward will have direct consequences for the

rare disease community. As part of the recommendations, the FDA is proposing a pilot program for supporting efficacy endpoint development for drugs that treat rare diseases by offering additional engagement opportunities with the agency to sponsors of development programs that meet specific criteria. The agency said that lack of regulatory precedent, small trial populations, and limited understanding of natural history associated with rare diseases creates unique challenges when determining the appropriate efficacy endpoints for clinical trials intended to evaluate the effectiveness of rare disease therapies.

The FDA also is proposing a new pilot program around real-world evidence to improve the quality and acceptability of real-world evidence-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements.

And the agency is proposing to strengthen staff capacity and capability to meet the increasing challenges of ensuring new cell and gene therapy products are developed and available to patients in a timely manner. It said increasing staff capacity will overcome existing resource limitations, allowing staff to spend additional time on meetings and submission reviews including those with breakthrough or regenerative medicine advanced therapy

U.S. FDA 2021 Biological License Application Approvals for Orphan Indications

Date	Trade Name	Proper Name	Indication
2/5/2021	Breyanzi	lisocabtagene maraleucel	Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.
3/26/2021	Abecma	idecabtagene vicleucel	Indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
6/4/2021	Ryplazim	plasminogen, human-tvmh	Indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemi).
6/15/2021	StrataGraft	Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat	Indicated for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns).
10/8/2021	Rethymic	Allogeneic processed Thymus Tissue	Indicated for immune reconstitution in pediatric patients with congenital athymia.

Source: U.S. Food and Drug Administration

designations, expand stakeholder outreach, invest in new policy and guidance, and facilitate development and use of regulatory tools and scientific technologies. Hyman, Phelps & McNamara's Valentine notes that the FDA's goal of 132 new hires for the Center for Biologics Evaluation and Research would represent a tripling of the equivalent hiring targets for the first fiscal year under PDUFA VI. In total for all fiscal years, the hiring commitments would equal a jump from 171 (PDUFA VI) to 228 (PDUFA VII) new staff in the Center for Biologics Evaluation and Research and 32 (PDUFA VI) to 123 (PDUFA VII) in Center for Drug Evaluation and Research. However, the hiring targets drop dramatically in both centers in each subsequent fiscal year after fiscal 2023.

"Every review component at the agency is understaffed and the poster child of being understaffed is the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research, the part of FDA that reviews all cell and gene therapies. If you think about gene therapy, the vast majority of those are for rare disease indications," Valentine said. "One of the overarching goals of PDUFA VII is to bolster the numbers and capacity of reviewers, particularly with a specific commitment to do so in OTAT. It's not a rare disease specific goal but to me that's incredibly important for rare diseases."

A Group of Innovative Orphan Drugs Win FDA Approval

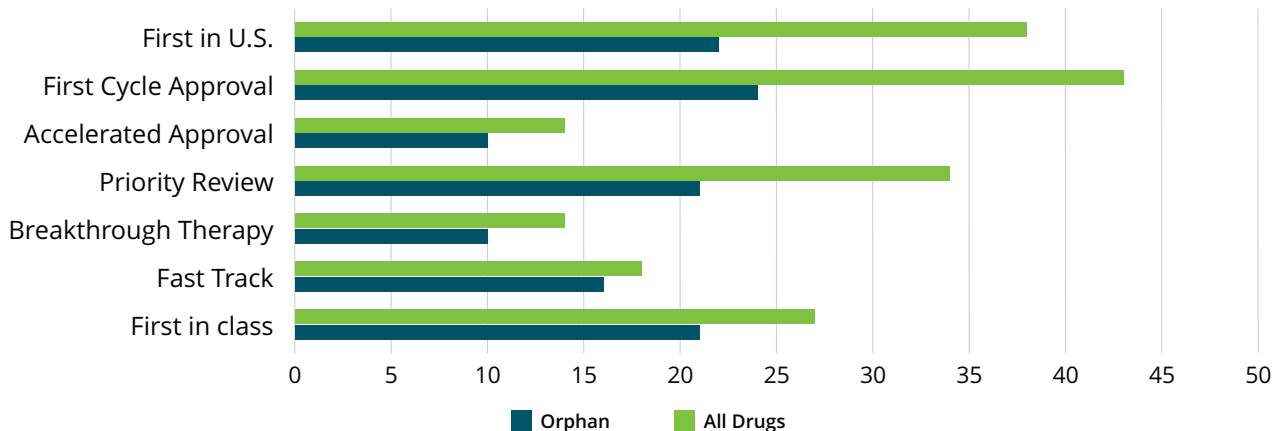
It was another solid year for orphan drug approvals in the United States. The U.S. Food and Drug Administration approved 26 novel orphan drugs in 2021, down from 31 novel orphan drugs (58 percent of the novel drug approvals) the previous year. Orphan drugs accounted for 52 percent of the total 50 novel drugs approved by the FDA's Center for Drug Evaluation and Research in 2021. Just less than half of the approvals were for rare forms of cancer.

A total of 21 of those drugs (81 percent) reflected first-in-class approvals, an indication of the strong innovation that is ongoing in the rare disease sector. A total of 22 of the orphan drugs won their first approval in the United States.

In a reflection of the disproportionate benefit rare disease therapies get from various FDA designations, 21 were approved with a Priority Review, 10 of the rare disease drugs won accelerated approval, 16 had Fast Track designations, 15 had Breakthrough Therapy designations.

Notable approvals in 2021 included PharmaEssentia's Besremi to treat adults with polycythemia vera, a rare, chronic, and life-threatening

U.S. Food and Drug Administration Novel Drug Approvals in 2021 by Designation



Source: U.S. Food and Drug Administration

FDA Should Look to Past Precedents When Applying Flexibility to Approvals to Maintain Public Trust

Though the U.S. Food and Drug Administration has flexibility in its approval criteria for drugs to treat life-threatening diseases with unmet needs, it lacks a way of weighing past decisions to provide a consistent standard for what constitutes adequate evidence in these cases, a new study finds.

Researchers at FDA and Stanford University conducted a study, which appeared in the *Annals of Internal Medicine* in September 2021. It comes in the wake of the controversy over the agency's approval of Biogen's Alzheimer's drug Aduhelm despite the fact that 10 of the 11 advisory committee members voted against recommending approval with one voting "uncertain" because of a lack of evidence that the drug was effective.

The FDA has had a long-established statutory requirement that there must be "substantial evidence" of a drug's effectiveness for it to approve its use. While there have been pathways and designations introduced to shorten drug development and the FDA approval process, largely in response to patients with unmet needs for life-threatening or rare diseases (orphan drug designation, fast track, accelerated approval pathway, priority review, and breakthrough therapy designation), the researchers note none of these designations or pathways formally change the "substantial evidence" requirement.

The FDA approved Aduhelm under the accelerated approval pathway on the basis of a surrogate endpoint, but the advisory committee felt the company failed to provide evidence of the endpoint's validity as a predictor of the drug's effectiveness.

In the study, the researchers sought to understand the FDA's evidentiary standards when flexible criteria are employed.

The researchers looked at applications submitted between 2013 and 2018 that went through multiple review cycles because the evidence for clinical efficacy was initially deemed insufficient. Of 912 applications reviewed, 117 went through multiple review cycles.



Of those, only 22 faced additional review primarily because of issues related to clinical efficacy.

Concerns about the endpoint, the clinical meaningfulness of the observed effect, and inconsistent results were common bases for initial rejection. In 7 of the 22 cases, the approval did not require new evidence but rather new interpretations.

The researchers found that the FDA has no mechanism to find, or tradition to cite, similar cases when weighing evidence for approvals. As a result, these decisions become standalone. In fact, the researchers found that the FDA uses highly variable criteria for "substantial evidence" when flexible evidential criteria are used.

The authors said the FDA has weak structures to support institutional memory, particularly one that crosses FDA therapeutic areas, offices, or centers. Much of it depends on staff memories and is lost with turnover. "This balkanization and fragility of institutional knowledge," they wrote, "diminishes institutional efficiency and consistency."

"A precedential tradition and suitable information system are required for the FDA to improve institutional memory and build upon past decisions," the authors wrote. "These would increase the FDA's decisional transparency, consistency, and predictability, which are critical to preserving the FDA's most valuable asset, the public's trust."

blood cancer caused by a mutation in stem cells in the bone marrow, which results in the overproduction of blood cells. When this occurs, it puts a person at risk for serious health problems, including blood clots, stroke and heart attack. Besremi is the only interferon approved for PV. It is a monopegylated, long-acting interferon that exhibits its cellular effects in polycythemia vera in the bone marrow. Besemri was approved with a boxed warning for risk of serious disorders including aggravation of neuropsychiatric, autoimmune, ischemic, and infectious disorders.



Two of the approvals in 2021 involved treatments for pruritus, an intense itching, associated with different rare liver diseases. Albireo won approval for Bylvay, the first drug approved for the treatment of pruritus in all subtypes of progressive familial intrahepatic cholestasis (PFIC). PFIC is a disorder that causes progressive liver disease and typically leads to liver failure. Bylvay is a potent, non-systemic ileal bile acid transport inhibitor, which does not require refrigeration and is easily administered as a once-daily capsule or opened and sprinkled onto soft foods.

The agency also approved Mirum Pharmaceutical's Livmarli to treat cholestatic pruritus in Alagille syndrome, an inherited condition in which bile builds up in the liver. It is the first and only FDA-approved medication for this rare liver disease that affects 2,000 to 2,500 children in the United States. Livmarli is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor.

Apellis Pharmaceuticals won approval for Empaveli, the first and only C3 targeted therapy to treat adults with paroxysmal nocturnal hemoglobinuria (PNH), a rare, life-threatening

blood disease. PNH is caused by an acquired mutation, which leads to uncontrolled complement activation and the destruction of red blood cells through intravascular and extravascular hemolysis.

Origin Biosciences won approval for Nulibry, the first therapy approved for molybdenum cofactor deficiency type A, an inherited disorder that typically presents in the first few days of life. The condition causes hard-to-control seizures, brain injury, and death.

Other notable approvals included BioMarin's Voxzogo to treat achondroplasia, the most common form of dwarfism; and Ascendis Pharma's Skytrofa for the treatment of pediatric patients one year and older who have growth failure due to inadequate secretion of endogenous growth hormone. Skytrofa offers patients an opportunity for once weekly treatment. Other approved human growth hormones require daily administration.

The FDA's U.S. Center for Biologics Evaluation and Research approved a total of 13 novel biologics in 2021, five of which carried orphan designations. This included Enzyvant's regenerative tissue-based therapy Rethymic for immune reconstitution in children born without a thymus. Rethymic (allogeneic processed thymus tissue-agdc) is the first and only treatment approved by the FDA for immune reconstitution in pediatric patients with the ultra-rare condition pediatric congenital athymia. Children with the condition are born without a thymus and have profound immunodeficiency, life-threatening immune dysregulation, and high susceptibility to potentially fatal infections as a result. Rethymic is engineered human thymus tissue designed to regenerate the thymic function children with congenital athymia are missing and does not require donor-recipient matching.

The agency also approved Liminal Biosciences' Ryzplazim the first approved treatment for patients with plasminogen deficiency type 1, also referred to as hypoplasminogenemia, a disorder that can impair normal tissue and organ function and may lead to blindness. ■

U.S. Food and Drug Administration Orphan Drug Approvals in 2021



Proprietary Name	Active Ingredient	Indication	Date	Designations
Amondys 45	casimersen	To treat Duchenne muscular dystrophy	2/25/2021	First-in-Class, Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Besremi	ropeginterferon alfa-2b-njft	To treat polycythemia vera	11/12/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Bylvay	odevixibat	To treat pruritus in progressive familial intrahepatic cholestasis	7/20/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Cytalux	pafolacianine	To use for ovarian cancer imaging	11/29/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Empaveli	pegretacoplan	To treat paroxysmal nocturnal hemoglobinuria	5/14/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Evkeeza	evinacumab-dgnb	To treat homozygous familial hypercholesterolemia	2/11/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Exkivity	mobocertinib	To treat types of locally advanced or metastatic non-small cell lung cancer	9/15/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
fexinidazole (approved without a trade name)	fexinidazole	To treat human African trypanosomiasis	7/16/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Livmarli	maralixibat	To treat cholestatic pruritus in Alagille syndrome	9/29/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Livtency	maribavir	To treat cytomegalovirus infection	11/23/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Lumakras	sotorasib	To treat types of non-small cell lung cancer	5/28/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Nexviazyme	avalglucosidase alfa-ngpt	To treat late-onset Pompe disease	8/6/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Nulibry	fosdenopterin	To reduce the risk of mortality in molybdenum cofactor deficiency type A	2/26/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Pepaxto	melphalan flufenamide	To treat relapsed or refractory multiple myeloma	2/26/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Rezurock	belumosudil	To treat chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	7/16/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Rylaze	asparaginase erwinia chrysanthemi (recombinant)- rywn	To treat acute lymphoblastic leukemia and lymphoblastic lymphoma in patients who are allergic to E. coli-derived asparaginase products, as a component of chemotherapy	6/30/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Scemblix	asciminib	To treat Philadelphia chromosome-positive chronic myeloid leukemia	10/29/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Skytrofa	lonapegsomatropin-tcgd	To treat short stature due to inadequate secretion of endogenous growth hormone	8/25/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Tavneos	avacopan	To treat severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis in combination with standard therapy, including glucocorticoids	10/7/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Tepmetko	tepotinib	To treat types of non-small cell lung	2/3/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Truseltiq	infigratinib	To treat cholangiocarcinoma	5/28/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Ukoniq	umbralisib	To treat marginal zone lymphoma and follicular lymphoma	2/5/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Voxzogo	vosoritide	To improve growth in children five years of age and older with achondroplasia and open epiphyses	11/19/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Vyvgart	efgartigimod alfa-fcab	To treat generalized myasthenia gravis	12/17/2021	Fast Track, Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Welireg	belzutifan	To treat von Hippel-Lindau disease	8/13/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.
Zynlonta	loncastuximab tesirine-lpyl	To treat types of relapsed or refractory large B-cell lymphoma	4/23/2021	Priority Review, Accelerated Approval, First Cycle Approval, First in U.S.

Source: U.S. Food and Drug Administration

A Good Year for Raising Money

Rare disease therapeutics developers raised capital at a record setting pace through initial public offerings in the first half of 2021, but a shift in financial activity during the second half of the year derailed IPO activity for rare disease companies with M&A taking center stage as Big Pharma demonstrated a growing appetite for rare disease companies.

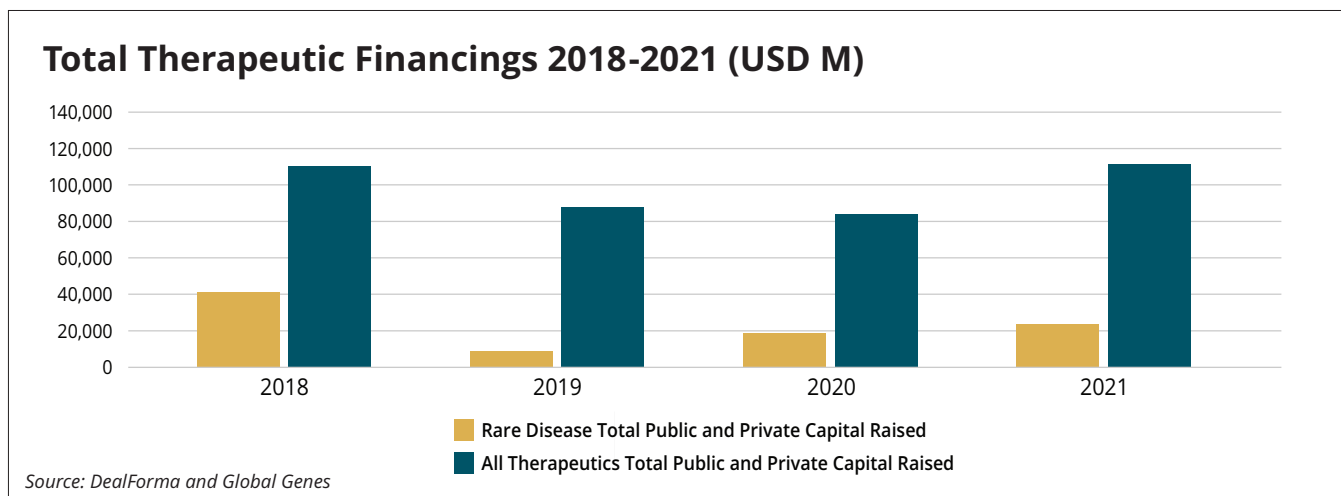
Overall, it was a difficult year for biotech stocks as *Evaluate Pharma* in November declared that the bubble burst for biotech stocks. It noted that “after a frothy couple of years, biotechs are no longer seeing big boosts from clinical data.” While the Nasdaq Biotech Index ended the year nearly unchanged, the SPDR Biotech ETF, an equally weighted exchange traded fund of biotech stocks, fell 20.4 percent. That compared to a 26.9 percent increase for the S&P 500 and a 21.4 percent gain for the NASDAQ.

Nevertheless, biotechnology companies were able to raise significant amounts of capital despite the overall weak

public market performance of the sector. In fact, rare disease financings were up in every category with the exception of IPOs, where there was a slight decrease in the total raised during the year. Overall, rare disease therapeutic developers raised a total of \$22.9 billion through public and private equity and debt financings in 2021. That grew 28 percent over the \$18 billion raised in 2020, according to data from DealForma and Global Genes.

Financing for all therapeutic companies including rare disease in 2021 rose to \$110.8 billion, a 32 percent increase from the \$83.7 billion raised the previous year. Rare disease drug developers accounted for 21 percent of all therapeutic financing activity in 2021, down from 27 percent in 2020.

The data in this report is focused solely on deals and financings of therapeutics developers. It is primarily taken from DealForma, a comprehensive biopharma database of deals and financings gathered daily using a combination of automation and hands-on curation,



Capital Raised by Rare Disease Therapeutics Companies to Date (USD M)

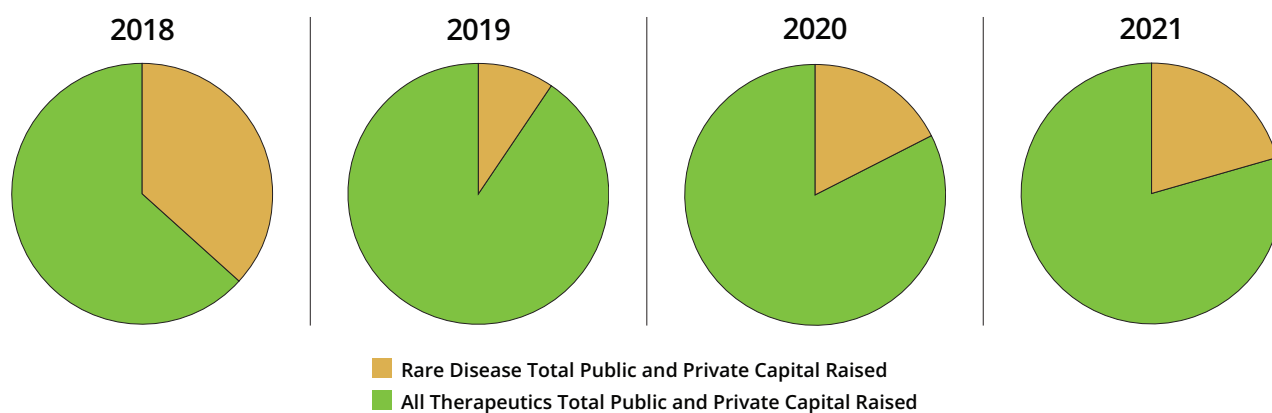
Deal Type	2021	2020	Change
Rare Disease Venture Capital	8,822	7,168	23.07%
All Therapeutics Venture Capital	39,974	23,766	68.20%
Rare Disease IPOs	4,309	4,495	-4.14%
All Therapeutics IPOs	14,969	13,007	15.08%
Rare Disease Public Equity and Debt (excl. U.S. IPOs)	9,786	6,303	55.26%
All Therapeutics Public Equity and Debt (excl. U.S. IPOs)	55,823	46,931	18.95%
Total Rare Disease Equity and Debt (Public and Private)	22,917	17,966	27.56%
Total All Therapeutics Equity and Debt (Public and Private)	110,766	83,704	32.33%
RD Partnering Deal Value at Signing	4,781	4,493	6.41%
All Therapeutics Partnering Value at Signing	14,935	18,030	-17.17%
RD Partnering Total Potential Deal Value	59,681	35,227	69.42%
All Therapeutics Total Potential Deal Value	158,884	152,838	3.96%
Rare Disease M&A Deal Value at Signing	49,437	58,915	-16.09%
All Therapeutics M&A Deal Value at Signing	83,354	126,488	-34.10%
RD M&A Total Potential Deal Value	53,228	63,784	-16.55%
All Therapeutics M&A Total Potential Deal Value	98,356	142,211	-30.84%

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

Rare Disease Total Financings as a Percent of All Therapeutics 2018 to 2020



Source: DealForma and Global Genes

which is supplemented and edited by Global Genes based on daily research and tracking of rare disease focused deals and financings. We define rare disease therapeutics developers as those companies advancing therapies for orphan indications or whose lead therapeutic candidate targets an orphan indication, and companies that devote a significant portion of their pipelines to orphan indications. In reality, the notion of rare disease is a regulatory construct and companies are often involved in developing therapies for both rare and more common conditions. In cases where it may not be clear to what extent a transaction involved rare diseases, the editors made judgment calls to include or exclude.

Rare Disease M&A Heats Up

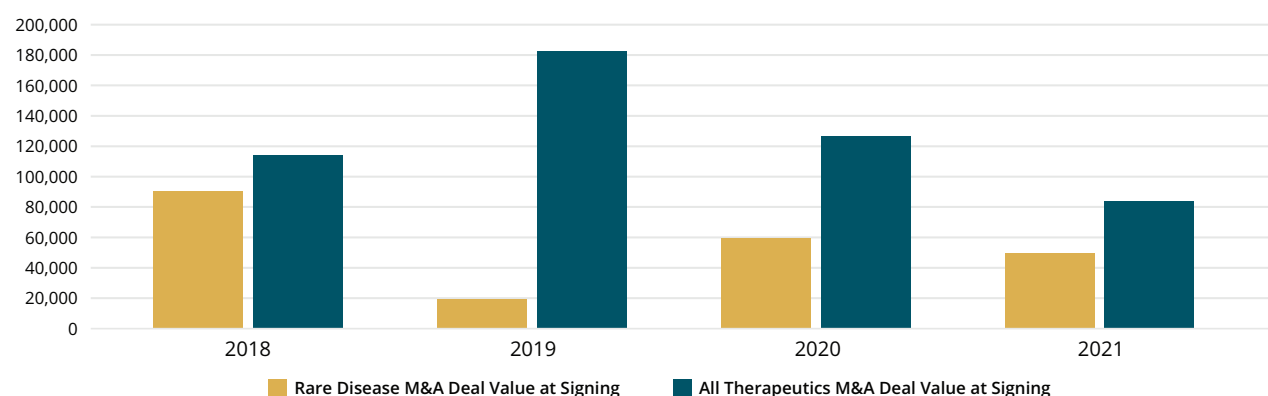
Rare disease therapeutic developers were the subject of 48 M&A transactions, one less than in 2020. Of those, 32 deals had disclosed values totaling \$53.2 billion, \$49.4 billion of which was paid at closing. Rare disease transactions accounted for 29 percent of all biopharma therapeutic M&A deals and for 54 percent of all reported M&A deal values in 2021. Overall, the biopharma therapeutic sector saw 167 M&A transactions with a total value of \$98.3 billion.

Though M&A activity fell short of record levels in the absence of blockbuster transactions that bolstered the overall numbers in 2018, 2019, and 2020, acquisitions of rare disease drug developers dominated the largest M&A deals of the year. In all, rare disease M&A transactions accounted for 59.3 percent of all therapeutic M&A deals in 2021, up from 22.8 percent excluding megadeals. In fact, seven of the ten largest transactions in 2021 involved rare disease companies as the target.

The largest M&A transaction in 2021 was CSL's \$11.7 billion acquisition of Vifor Pharma. The deal provides CSL with a high-growth, cash generating business that complements and expands CSL's two business units. It adds a portfolio of products across nephrology, dialysis, and iron deficiency therapies.

Merck's purchase of Acceleron was a close second in the list of top acquisitions at \$11.5 billion. The deal moves Merck strongly into the rare disease space. Merck said it complements and strengthens its cardiovascular pipeline. Acceleron's lead therapeutic candidate, sotatercept, has a novel mechanism of action with the potential to improve short-term and/or long-term clinical outcomes in patients with pulmonary arterial hypertension (PAH), a rare, progressive and life-threatening blood vessel disorder. Sotatercept is in phase 3 trials as an add-on to current standard of care for the treatment of PAH.

Therapeutic M&A Deals at Signing (USD M) 2018-2021



Source: DealForma and Global Genes



While the largest acquisitions in the rare disease space generally involved Big Pharma acquirers, large, rare disease focused companies also looked to acquisitions to expand their pipelines and product offerings through sizable purchases. Jazz Pharmaceuticals acquired GW Pharmaceuticals for \$7.2 billion and Horizon Therapeutics acquired Viela Bio for \$3.1 billion.

Jazz's acquisition of GW bolsters its neuroscience pipeline by adding GW Pharma's proprietary cannabinoid product platform that addresses a broad range of rare diseases. GW Pharma's Epidiolex is the first plant-derived cannabinoid medicine ever approved by the U. S. Food and Drug Administration for use in patients one-year and older to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and Tuberous Sclerosis Complex, all of which are rare diseases characterized by severe early-onset epilepsy. It is also approved in the European Union in patients two years of age and older for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in conjunction with clobazam and is under EMA review for the treatment of seizures associated with TSC.

For Horizon, the acquisition of Viela Bio adds Uplizna to the company's product offerings.

Uplizna won approval in June 2020 for the treatment of adults with the rare autoimmune condition neuromyelitis optica spectrum disorder (NMOSD), a severe neuro-inflammatory disease that attacks the optic nerve, spinal cord, and brain stem. In addition to potentially irreversible blindness and paralysis, patients may also experience loss of sensation, bladder and bowel dysfunction, nerve pain and respiratory failure.

Sanofi was the most active company on the rare disease M&A front with three deals with a combined value of \$5.6 billion. This includes Sanofi's \$1.9 billion acquisition of Kadmon Holdings, which gave it Rezurock, the approved, first-in-class therapy for the treatment of chronic graft-vs-host disease; the acquisition of Tidal Therapeutics, which has an mRNA-based platform for immuno-oncology and inflammatory disease for \$160 million up front and up to \$310 million in milestones; and its \$3.2 billion acquisition of mRNA therapeutics developer Translate Bio. Though Sanofi was already working with Translate Bio on applying its mRNA technology to develop vaccines, the company's lead therapeutic candidate is for the rare pulmonary disease cystic fibrosis, and Sanofi is interested in applying its platform to rare diseases as well as immunology, oncology, and vaccines.

Partnering Accelerates

The total value of partnering deals involving rare disease therapeutics rose in 2021 to a total potential value of \$59.7 billion, up from \$35.2 billion in 2020. The total disclosed value at closing rose to \$4.8 billion, up from \$4.5 billion in 2020. The number of rare partnering deals totaled 180, up from 135 in 2020.

The activity in the rare disease space grew relative to the overall biopharma therapeutic partnering activity. In 2021, rare disease deals accounted for 38 percent of the \$158.9 billion in total potential value of partnering deals announced in 2021, up from 23 percent of the \$153.8 billion announced in 2020.

Similarly, the value of rare disease partnering deals at signing rose to 37 percent of the \$15 billion in all biopharma therapeutics partnering deals announced in 2021, up from 25 percent of the \$18 billion in announced deals for the same period a year ago.

Takeda Pharmaceutical was the most active company on the rare disease partnering front with a total of 12 transactions, eight of which had disclosed values. The total potential value of those transactions topped \$10 billion with the upfront cash and R&D portion approaching \$1.1 billion. These transactions included the largest potential value of any life sciences therapeutic partnering deal in 2021, a broad collaboration

with Poseida Therapeutics to use its DNA and RNA nanoparticle delivery technology and other genetic engineering platforms for the research and development of up to eight gene therapies with a focus on non-viral *in vivo* gene therapy programs including Poseida's hemophilia A program. The deal included \$45 million in upfront payments and up to \$3.6 billion in potential milestone payments.

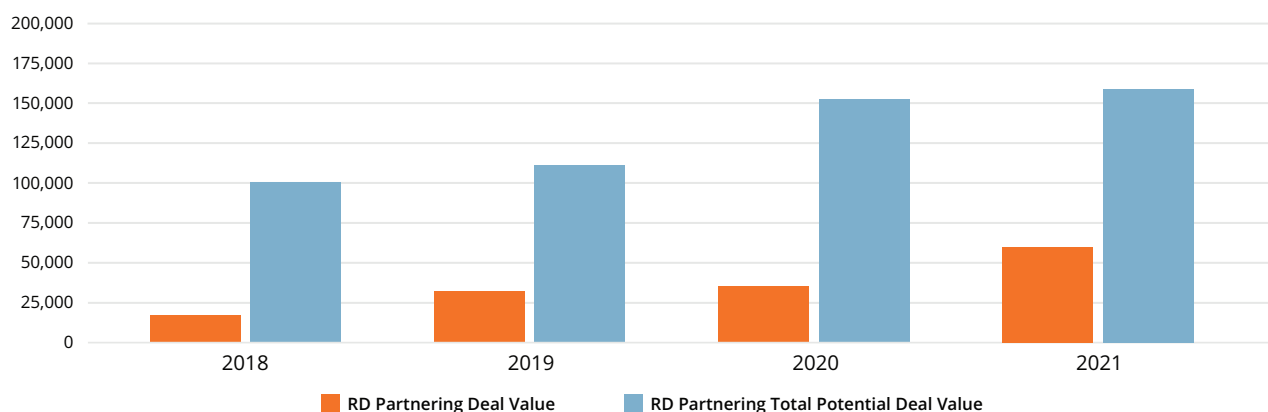
In fact, genetic medicines accounted for about a third of all rare disease partnering deals with 40 gene therapy deals, 12 gene editing deals, 9 RNA deals, four vector deals, and an mRNA deal. Access to new modalities were not the sole driver of these agreements. A total of 36 partnering deals centered on small molecule drugs.

Gene Therapy Dominates Venture Deals

The rare disease therapeutic sector set a new record for venture capital financing as the sector raised a total of \$8.8 billion, up from the \$7.2 billion raised in 2020. In a reflection of the large amounts of capital available through venture financings a total of 29 of the rare disease rounds exceeded \$100 million, up from 22 a year ago and just six in 2018.

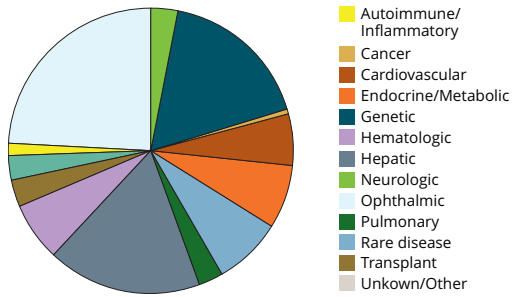
While the number of series A deals fell to 39 in 2021 from 45 a year ago, there continued to be

Total Potential Value of Partnering Deals 2018 to 2021 (USD M)



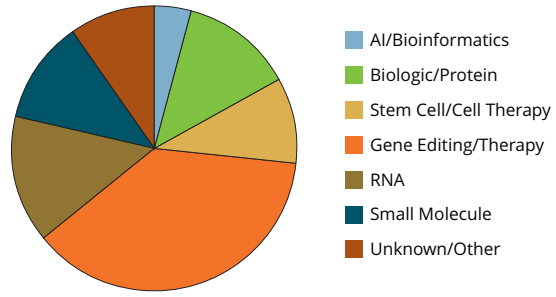
Source: DealForma and Global Genes

2021 Rare Disease Venture Financing by Indication, (USD M)

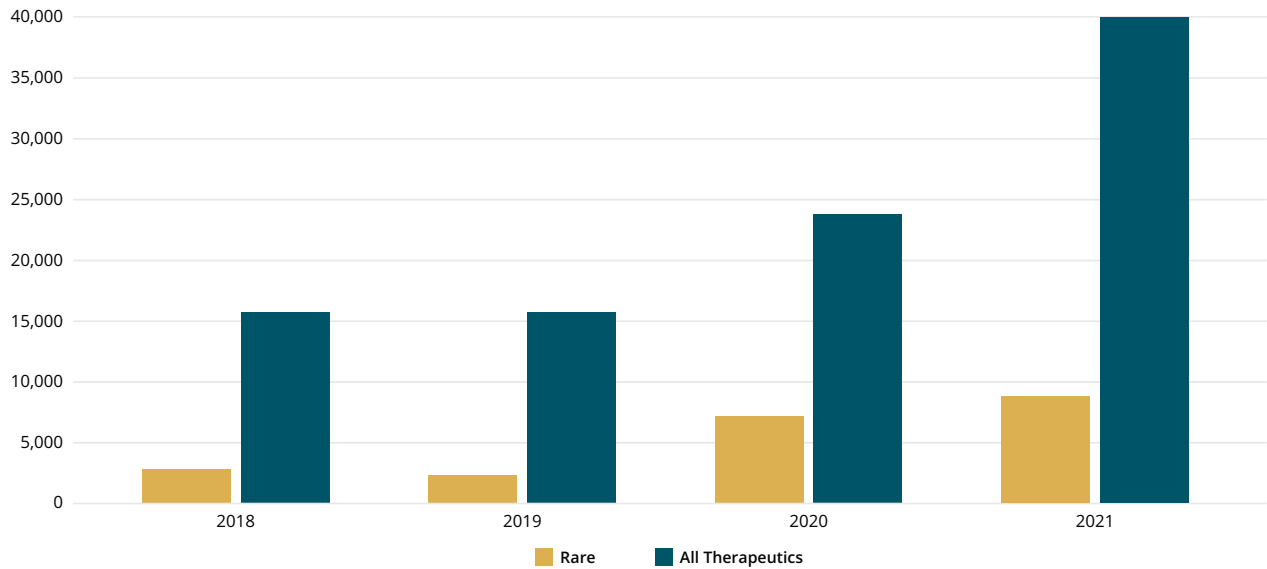


Source: DealForma and Global Genes

2021 Rare Disease Venture Financing by Platform Technology, (USD M)

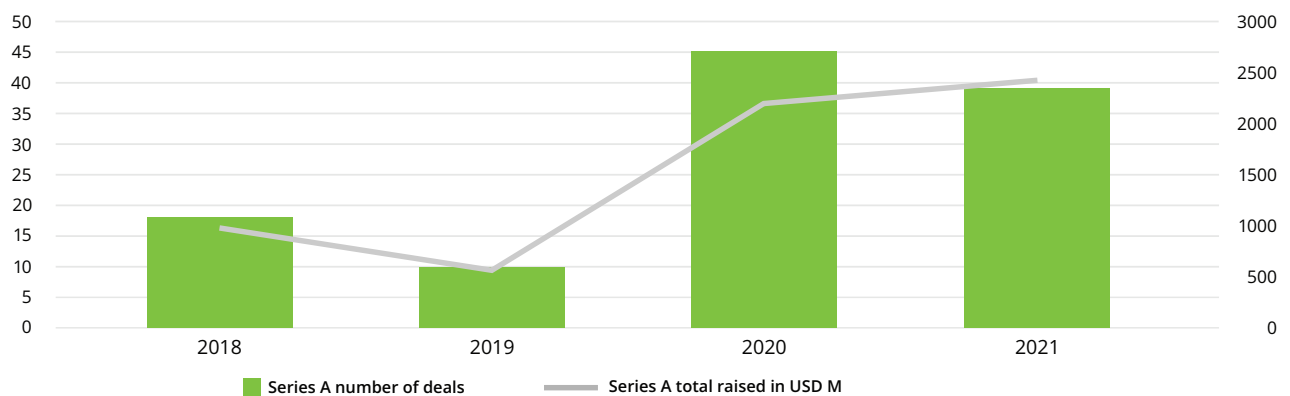


Venture Capital Financing for Therapeutics 2018-2020 (USD M)



Source: DealForma and Global Genes

Rare Disease Series A Venture Round



Source: DealForma and Global Genes

a strong appetite for early-stage deals. In fact, rare disease drug developers raised \$2.4 billion in series A financings in 2021, up from the \$2.2 billion raised in series A financings for the same period a year ago. Overall, series A rounds accounted for 27.2% of the total venture capital raised by rare disease drug developers in 2021.

The average venture funding for rare disease therapeutics developers reached \$83.2 million in 2021, up from \$74.7 million a year ago. Cell and gene therapy developer ElevateBio, which is developing treatments for cancer and rare diseases, closed the largest rare disease financing round of the year with a \$525 million series C round.

G2 Bio Companies, whose founders include gene therapy innovator James Wilson and the University of Pennsylvania Gene Therapy Program, closed the largest series A financing of the year with a \$200 million investment made by the Singapore-based investment company Temasek to fund its launch.

Another Big Year for IPOs

Overall, therapeutics developers raised a record \$15 billion through 100 initial public offerings in 2021, up from 76 IPOs that raised \$13 billion for the same period a year ago. Never-

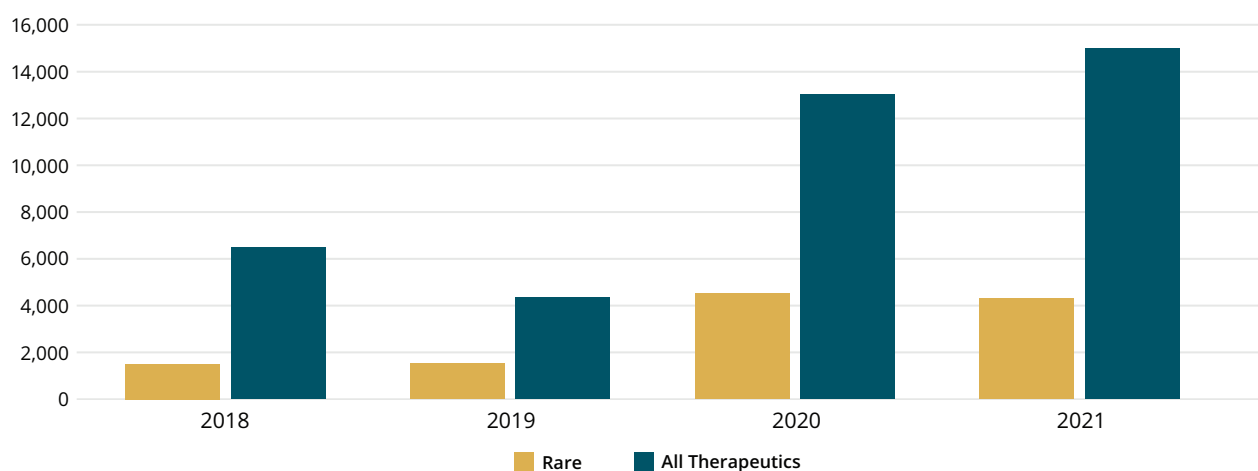
theless, rare disease drug developers had a drop in IPO activity in 2021, raising a total of \$4.3 billion in 23 IPOs in 2021, down from \$4.5 billion in 25 deals the previous year.

The year was on a record setting pace during the first half of 2021. A total of 17 of the rare disease IPOs were completed by June 30 and accounted for \$3.4 billion or 79 percent of the total raised during the year. Average IPO deal sizes in the first half of the year totaled \$200.2 million. That compared to an average of \$108.7 for rare disease IPOs in the second half of 2021.

While 17 rare disease IPOs finished their first day of trading above their initial offering price, two companies—Vor Biopharma and Design Therapeutics—more than doubled their price in the first day of trading. Nevertheless, 17 of the 23 rare disease companies that went public in 2021 ended the year with their shares trading below their initial offering prices. Only six issues ended the year higher. Overall, rare disease new issues on average fell 11.1 percent compared to a 10.6 percent gain in 2020.

Vera Therapeutics, a clinical stage company focused on immunologic diseases with a lead experimental therapy for autoimmune kidney disease IgA nephropathy, was the biggest gainer on the year. It ended at \$26.72, up 142.9 percent at year end.

Therapeutic Developer IPOs 2018 to 2021 (USD M)



Source: DealForma and Global Genes

Rare Disease Therapeutics IPOs on U.S. Exchanges in 2021

Date Completed	Location	Company	Ticker	Total Raised (\$M)	Shares Sold (M)	Price Per Share (\$)	Description	Stage	First Day Price Change	Offering Price	Share Price 12/31/2021	Change since IPO (12/31/21)
2/4/2021	U.S.	Sana Biotechnology	SANA	675.6	27	25	Engineered cell therapies	Preclinical	40%	25	15.48	-38.1%
2/4/2021	U.S./Netherlands	Pharvaris	PHVS	190.2	9.5	20	Small molecule Rare disease therapies	Phase 1	45%	20	14.39	-28.1%
2/5/2021	U.S.	Vor Biopharma	VOR	203.4	11.3	18	Hematological cell therapies	Preclinical	108%	18	11.62	-35.4%
2/11/2021	U.S.	Decibel Therapeutics	DBTX	127	7.1	18	Gene therapies for disorders of ear	Phase 1	0%	18	4.65	-74.2%
3/12/2021	U.S.	Longboard Pharmaceuticals	LBPH	80	5	16	Rare neurological diseases small molecules	Phase 1	4%	16	4.84	-69.8%
3/18/2021	U.S.	Gain Therapeutics	GANX	46	3.6	11	Lysosomal storage disorders	Preclinical	2%	11	5.34	-51.5%
3/26/2021	U.S.	Design Therapeutics	DSGN	276	13.8	20	Rare disease small molecule therapies	Preclinical	107%	20	21.41	7.0%
3/26/2021	U.S.	Edgewise Therapeutics	EWTX	202.4	12.7	16	Rare muscle disorders	Phase 1	88%	16	15.28	-4.5%
4/9/2021	U.S.	Reneo Pharmaceuticals	RPHM	93.8	6.3	15	Mitochondrial diseases	Phase 2	-7%	15	8.55	-43.0%
4/9/2021	U.S./Switzerland	VectivBio	VECT	146.6	8.6	17	Rare GI disorders	Phase 3	43%	17	4.91	-71.1%
4/16/2021	U.S.	Recursion Pharmaceuticals	RXRX	501.8	27.9	18	AI therapies for rare diseases	Phase 2	74%	18	17.13	-4.8%
5/7/2021	U.S.	Talaris Therapeutics	TALS	150	8.8	17	Allogeneic cell therapies for transplantation	Phase 3	-4%	17	15.29	-10.1%
5/14/2021	U.S.	Vera Therapeutics	VERA	47.9	4.4	11	Immunology-Renal-IgAN	Phase 2b	5%	11	26.72	142.9%
5/27/2021	U.S.	Day One Biopharmaceuticals	DAWN	184	11.5	16	Pediatric and genetically defined cancers	Phase 2	62%	16	16.85	5.3%
6/17/2021	U.S.	Verve Therapeutics	VERV	306.7	16.1	19	Cardiovascular gene editing	Preclinical	68%	19	36.87	94.1%
6/25/2021	U.S.	Graphite Bio	GRPH	273.7	16.1	17	Gene editing	Phase 1	9%	17	12.43	-26.9%
6/29/2021	U.S.	Aerovate Therapeutics	AVTE	139.8	10	14	Inhaled formulation for PAH	Phase 2	63%	14	11.79	-15.8%
7/15/2021	U.S.	Imago Biosciences	IMGO	134.4	8.4	16	Rare bone cancers	Phase 2	2%	16	23.71	48.2%
7/29/2021	U.S.	Rallybio	RLYB	92.7	7.1	13	Rare diseases antibody therapies	Phase 1/2	-7%	13	9.54	-26.6%
7/30/2021	U.S.	Tenaya Therapeutics	TNYA	207	13.8	15	Cardiovascular	Preclinical	2%	15	18.95	26.3%
10/29/2021	U.S.	Entrada Therapeutics	TRDA	182	9.1	20	Rare neuromuscular diseases	Preclinical	20%	20	17.12	-14.4%
12/8/2021	U.S./Israel	NeuroSense Therapeutics	NRSN	12	2	6	Neurodegenerative ALS	Phase 2		6	2.45	-59.2%
12/15/2021	U.S./Italy	Genenta Science	GNTA	36	3.1	11.5	Stem cell gene therapy for cancer	Phase 1/2	-4%	11.5	10.96	-4.7%

Source: DealForma and Global Genes

Decibel therapeutics, which is developing gene therapies for disorders of the ear, ended the year at \$4.65, a 74 percent drop from its initial offering price of \$18.00. The company's lead experimental therapy is a gene therapy for treatment of hearing loss caused by a mutation to the OTOF gene. The preclinical program is being developed in partnership with Regeneron.

Sana Biotechnologies, a developer of engineered cell therapies, completed the largest IPO of the year. The company raised a total of \$676 million through the sale of 27 million shares. The offering came at \$25 a share, above its initial target range of \$20 to 23 a share. The company is seeking to repair and control genes, replace missing or damaged cells, and make its therapies broadly available to patients. It is building a pipeline of both *in vivo* and *ex vivo* treatments targeting rare and more common indications in oncology, hematology, metabolic, and neurology. Targets include multiple myeloma, acute and chronic lymphocytic leukemia, liver-related genetic disorders, hemoglobinopathies, type 1 diabetes, Huntington's disease, and heart failure, among others.

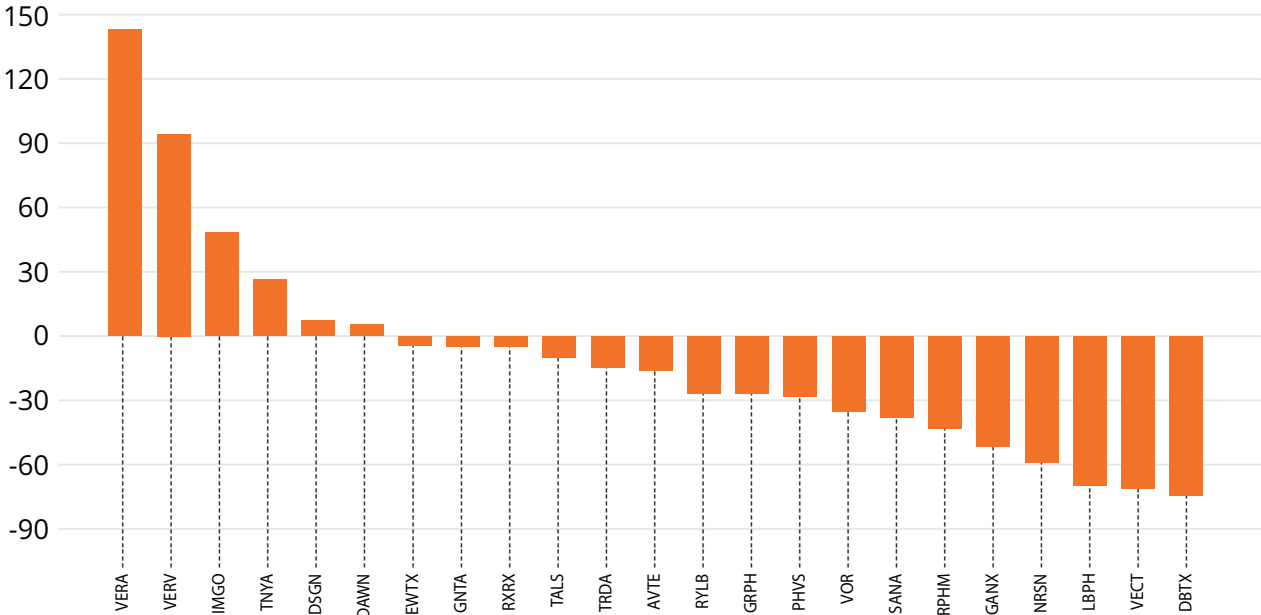
Sana said proceeds from the financing will be used to advance discovery and development within the company's core platforms, including gene delivery, immunology, stem cell biology, and gene modification and control. Some approaches include *in vivo* delivery of genetic payloads to specific cells, *ex vivo* genetic modifications that hide allogeneic cells from a patient's immune system, and applying stem cell biology to make differentiated cells to replace missing or damaged tissue.

Public Finance Soars

Rare disease companies last year raised \$9.8 billion in public equity (excluding IPOs) and debt offerings, a 55.3 percent increase over the \$6.3 billion raised in 2020. That represented about 18 percent of the total \$55.8 billion raised by therapeutic developers in 2021, up from 13 percent of the \$46.9 billion raised the previous year.

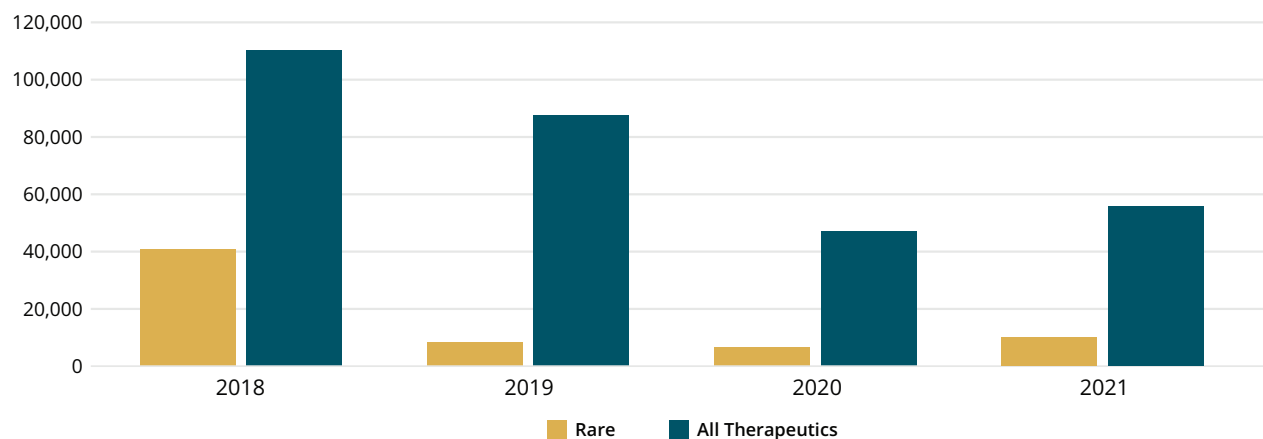
Gene therapy platform company Intellia Therapeutics raised \$690 million in a secondary offering in June. The company has two early-

Aftermarket Performance of 2021 Rare Disease Therapeutics IPOs (12/31/21)



Source: DealForma and Global Genes

Public Therapeutics Debt and Equity Financings Excluding IPOs 2018 to 2021 (USD M)



Source: DealForma and Global Genes

stage clinical programs, one partnered with Regeneron in ATTR amyloidosis and the other in hereditary angioedema. Intellia priced the offering at \$145.00 per share. The offering followed the release of data from Intellia and Regeneron that supported the efficacy of *in vivo* CRISPR genome editing in humans.

The two companies reported that in a phase 1 dose escalation study in patients with transthyretin (ATTR) amyloidosis, a rare, progressive, and deadly disease in which mutations in the TTR gene cause the liver to produce misshapen transthyretin (TTR) protein that misfold and build up as amyloid in the body, a single intravenous infusion with Intellia's NTLA-2001 led to dose-dependent reductions in serum TTR, with mean reductions of 52 percent among the three patients in the low dose group, and 87 percent among the three patients in the high dose group, including one patient with a 96 percent reduction.

NTLA-2001 is the first experimental CRISPR therapy candidate to be administered systemically to edit genes inside the human body. Intellia uses lipid nanoparticles to deliver a two-part genome editing system to the liver—a guide RNA specific to the disease-causing gene and a messenger RNA that encodes the Cas9

enzyme, which carries out the precision editing. CRISPR has already been used effectively to treat sickle cell disease and beta-thalassemia, but in those cases, the gene editing took place outside the body, with the edited gene then being inserted back into the body.

Rare disease companies raised a total of \$1.7 billion through debt offerings in 2021, up from \$6.3 billion a year ago. BridgeBio was the largest debt issuer in the rare disease sector raising \$1.1 billion through two offerings.

The Year Ahead

Despite the tumultuousness of the public market trading activity for biotech stocks, companies continue to have a strong allure to investors and are able to raise large amounts of capital to advance their pipelines.

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. ■

Treatment

Understanding the Costs of Rare Disease



“Most persons living with a rare disease around the world are at the margins of society, unrecognized, stigmatized, and discriminated.”

— *Durhane Wong-Rieger, president and CEO of the Canadian Organization for Rare Disorders and RDI Council*

When Elle Dicks was about 10 months old, she developed a stomach virus. When she recovered, she had difficulty swallowing food that she put into her mouth. By 12 months of age, she wasn't growing. When she went for her 15-month medical visit, she was eating little, spitting out most of what entered her mouth, drinking lots of water, and not gaining any weight. Her parents said she had been a bright star, but she was slowly beginning to dim.

It would take about two and a half years for the Dicks to learn what was wrong with Elle. Doctors finally diagnosed her with the rare lysosomal storage disorder cystinosis. People with cystinosis are unable to break down food properly due to an enzyme deficiency. As a result, they develop an accumulation of the amino acid cystine in various organs and tissues of the body, such as the kidneys, eyes, muscles, pancreas, and brain. The disease can cause kidney failure, muscle wasting, swallowing difficulty, diabetes, hypothyroidism, cerebral atrophy, blindness, difficulty breathing, and more. Without treatment, children with cystinosis will develop end-stage kidney failure and die prematurely. The condition affects

an estimated 2,000 people worldwide with just more than 600 of those diagnosed living in the United States.

While the disease took a toll on Elle's physical condition, it also took one on the Cincinnati family's financial health as well. Her mother Shirley, a teacher who specializes in early intervention for children on the autism spectrum, had to cut back her hours to three days a week. Elle's father Jon, an emergency room nurse who worked 12-hour night shifts plus overtime that put him between 60 and 70 hours a week, found he could no longer perform the intensive work without distraction. He's now studying to become a licensed nurse practitioner and in the meantime is working about 25 hours a week as a personal trainer and fitness coach at a gym he opened with three friends.

While the Dicks had health insurance through Shirley's job, the family quickly found many of Elle's needs required a significant investment of time to arrange and coordinate. She sees a number of specialists including a nephrologist, gastroenterologist, ophthalmologist, and genetic counselor. In addition to her medical care, there is a set of adjunctive care she requires and that the family must pay for out-of-

pocket including physical therapy, occupational therapy, and myofunctional therapy to help her with swallowing.

Though their insurance covers the bulk of the cost of her expensive cystine reducing therapy, she also requires electrolyte replacement therapy and special medical foods a local hospital prepares for her that are fed through a G-tube, which is only partially covered. The family has had to pay for certain medical equipment too. And, they have had to absorb the cost for needed modifications to their home, such as a water filtration system because Elle drinks two to three gallons of water a day because of her condition, and must have the fluoride removed.

"You get creative, and you learn to budget. We had to figure out what was extraneous for us. Anywhere we can try to save some money we do," said Elle's father Jon Dicks. "We're also very active in searching for different avenues to be able to get some of this covered. There are places that you can go to get certain amounts of your co-pay back."

While the family has been able to get some financial support from a nonprofit organization, it has also turned to a GoFundMe campaign in anticipation of Elle eventually needing a kidney transplant for which they will need to come up with a 20 percent co-pay. Home modifications were all out-of-pocket.

To people who don't know Elle, she looks like pretty much any child. Her kidney disease, the muscle pain, and fatigue are not visible. "Without the tubes, a wheelchair, or the team of people who work with Elle, it can be difficult for people to understand all it takes to care for her. A lot of people look at her and don't think that there's all that much that goes into this," said Dicks. "It's truly the adage of never judging a book by its cover. This little girl has a host of people behind her."

The Financial Toll of Rare Disease

Data around rare diseases has always been challenging. It has been difficult to reach agreement on the number of rare diseases or say with precision how many people suffer from these conditions. That's a challenge that's related to the rarity of these diseases, the difficulty of diagnosing people with these conditions, and mechanisms for tracking patients with rare diseases in the healthcare system. Understanding the economic burden of these disorders is doubly challenging because not only are most rare conditions without assigned codes to enable the tracking of medical spending, but also many of the costs associated with living with these diseases fall outside the direct cost of care that can be captured through electronic medical records and claims databases.

"We had to figure out what was extraneous for us. Anywhere we can try to save some money we do."

—Jon Dicks



Burden of Chronic Diseases Estimate

Condition	Source	Burden Estimates
Diabetes	American Diabetes Association (2017)	\$327 billion (2017)
Cancer		Projected \$174 billion in 2020
Heart disease and stroke	Benjamin et al (2018)	\$214 billion (2018)
Obesity	Finkelstein et al (2009)	\$147 billion (2008)
Arthritis	CDC (2013)	\$304 billion (2013)
Alzheimer's disease	Hurd et al (2013)	Between \$159 billion and \$215 billion (2010)

Source: U.S. Centers for Disease Prevention and Control and Yang, Grace, et al.; *The National Economic Burden of Rare Disease Study*, February 25, 2021, https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf?eType=E-mailBlastContent&eld=1d1fcfbd-10fc-4553-bf38-dfd73c7e7cd8

As researchers have sought to understand these costs better, they have found that healthcare costs for people with a rare disease have been underestimated. In fact, a 2021 study in the *Orphanet Journal of Rare Diseases* found these costs are three to five times greater than the costs for people without a rare disease.¹⁵ The study suggests that nationwide medical costs for individuals with rare diseases are on par with those for cancer and heart failure.

Researchers analyzed patients' diagnosis information in medical records and billing codes. They used International Classification of Diseases (ICD) codes, which designate a disease diagnosis, and other methods to determine those individuals with rare diseases and their direct medical costs for 14 rare diseases in four health care systems compared to non-rare disease patients of a similar age.

The team determined approximate medical costs by examining healthcare system data from the National Center for Advancing Translational Sciences and Eversana, a provider of commercial services to the pharmaceutical industry. In every case, the cost per patient per year for those with a rare disease exceeded costs for non-rare disease patients of the same age. According to the Eversana healthcare system database, which included estimates from commercial and insurance payors over nearly 15 years, the cost per patient per year ranged from \$8,812 to \$140,044 for rare disease patients compared to \$5,862 for those without a rare disease. The NCATS data, which drew from estimates mostly from Florida Medicaid information over five years, indicated the cost per patient per year ranged from \$4,859 to \$18,994 for rare disease patients versus \$2,211 for those without a rare disease.

The team reported that extrapolating the average costs estimate for the approximately 25 to 30 million individuals with rare diseases in the United States would result in total yearly direct medical costs of approximately \$400 billion, which is similar to annual direct medical costs for cancer, heart failure, and Alzheimer's disease.

In reality, the cost of rare diseases extends well beyond direct medical spending. While some studies have sought to calculate the cost around specific rare diseases, a separate 2021 study, developed by the EveryLife Foundation for Rare Diseases sought to make what it calls the most comprehensive assessment of the total cost of rare disease in the United States to date.



The National Economic Burden of Rare Disease Study found that the total costs in 2019 of rare disease in the United States was just shy of \$1 trillion.¹⁶ The EveryLife Foundation for Rare Diseases commissioned the healthcare and human services policy analytics and consulting firm Lewin Group to calculate the economic impact of rare disease in the United States in 2019. More than a dozen pharmaceutical companies developing therapies for rare diseases funded the study.

The authors said their calculations are conservative and cover an estimated 15.5 million people in the United States with 379 rare diseases. While the diseases used in the study included some of the most prevalent rare diseases, it also included some ultra-rare diseases. The \$966 billion in 2019 that they calculated surpasses the economic burden estimates for many of the costliest chronic diseases, including diabetes, heart disease, and cancer.

Annie Kennedy, chief of policy and advocacy at the EveryLife Foundation, noted that the numbers show that rare diseases represent an “urgent public health crisis that demands additional research, enhanced awareness, and improved access to diagnosis, care, and treatment.”

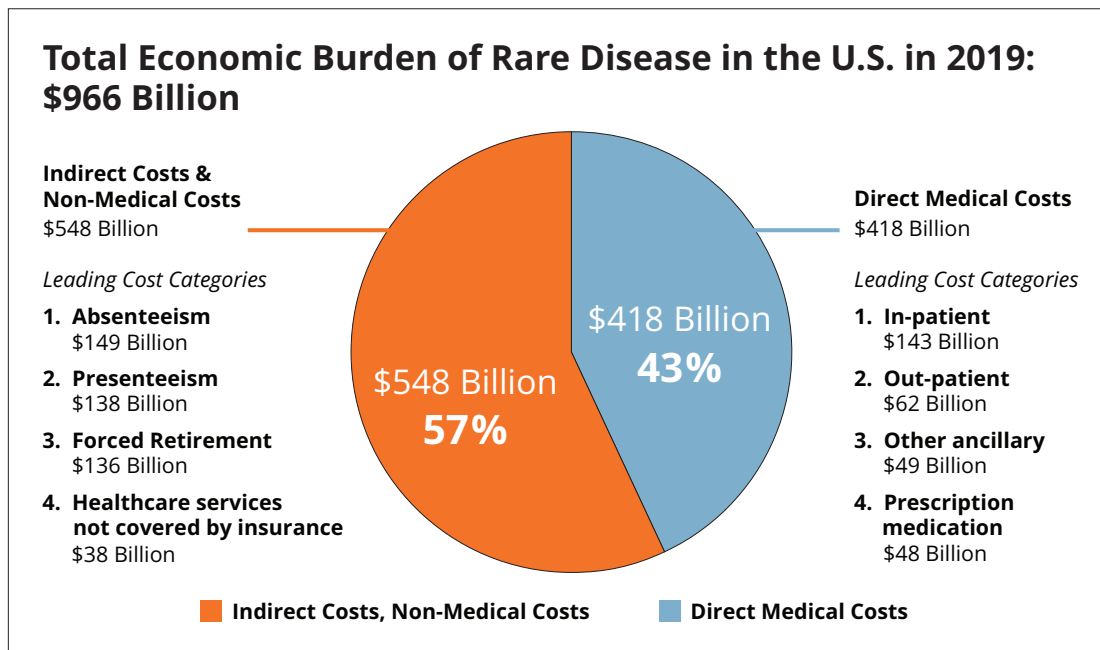
“If you’re a family living with a rare disease, the considerations are often based on direct costs data, the costs that are showing up in your physician visits, your ER admissions, your prescriptions,” said Kennedy. “That to me is the tip of the iceberg—what we can see above the water surface. The cost that we don’t see in the public domain are all those costs under the water surface, all those costs that are absorbed by families, but don’t get counted in the broader public health domain.”

The study looked at the non-medical costs including the out-of-pocket costs for medical foods and nutrition, costs for home renovations for needed modifications for accessibility as conditions progress, durable medical equipment, and the absorbed costs because you are no longer in the workplace and you’ve had to retire early, or you are not working full time because you are a care giver or you yourself have a disability due to your diagnosis.

“Those costs were things that were very important to us to calculate as part of this study and to bring into the broader discussion around rare disease overall and around what it means to be living with a rare disease to individuals, to families, and to the broader public,” she said.

“The cost that we don’t see in the public domain are all those costs under the water surface, all those costs that are absorbed by families.”

—Annie Kennedy



Source: Yang, Grace, et al.; *The National Economic Burden of Rare Disease Study*, February 25, 2021, https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf?eType=EmailBlastContent&eid=1d1fcfbd-10fc-4553-bf38-dfd73c7e7cd8

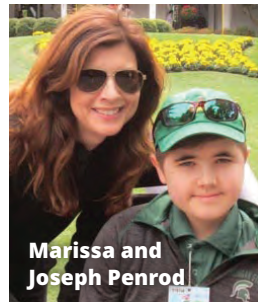
Researchers combined the prevalence of rare diseases with per capita costs to derive the national economic burden. To estimate prevalence and the direct medical cost, the study evaluated claims data from Medicare, Medicaid, and the Optum de-identified Normative Health Information System, a large and geographically diverse claims database for the privately insured.

The study also included a primary survey designed to deepen the understanding of the full spectrum of the impact of rare disease in the United States. The survey, which included 1,399 fully completed responses from individuals representing about 379 rare disease communities, collected detailed data on a broad set of indirect and non-medical costs of rare disease that were previously unavailable, especially the impact of rare disease on unpaid caregivers.

The total the researchers calculated included \$418 billion (43 percent) in direct medical costs. Direct medical cost consists of such things as expenditures for inpatient hospital or outpatient care, physician visits, prescription medications, and durable medical equipment. The \$548 billion in indirect and non-medical costs includes lost productivity due to forced retirement, absenteeism, and presenteeism (when people show up to work but don't function fully), as well as social productivity loss in community participation and volunteer work.

Also included in the indirect costs are healthcare services not covered by insurance. These include experimental treatments, alternative and non-traditional treatments, medical foods, and dental surgeries. Non-medical costs include paid daily care, necessary home and vehicle modifications, transportation costs, home schooling, missed schooling, and special education.

"For many families, the journey begins with the search for a diagnosis and hope for an effective treatment. It very quickly evolves into navigating a complex medical system, engaging in battles with insurance companies, and paying out-of-pocket for necessary home and vehicle modifications," said



Marissa and Joseph Penrod

Marissa Penrod, mother of a son with a rare disease, founder of Team Joseph, and advisor to the study team. "This all happens within the typical demands of a family, while trying to hold down a job and maintain some quality of life. This report should be a call to action. We can do more to help our families, and we must."

Navigating Bureaucracy

One of the invisible costs of rare diseases is the time patients and caregivers must spend navigating the bureaucracy of payers to secure treatment and reimbursement. A July 2021 study, in the *Orphanet Journal of Rare Disease*, looked at the experiences of parents navigating the U.S. health insurance landscape for children with a rare disease.¹⁷ For the study, researchers in the Department of Health Promotion and Policy at the School of Public Health and Health Sciences at the University of Massachusetts, Amherst conducted semi-structured interviews with parents of children with the neurodegenerative condition metachromatic leukodystrophy (MLD) and spinal muscular atrophy (SMA). The researchers chose those conditions because of specific disease characteristics and orphan drug status.

One woman who participated in the study told how, because she knew she was giving birth to a child with spinal muscular atrophy, a rare and progressive neuromuscular condition, she declined anesthesia because she wanted to be sure that as soon as the child was delivered, she could complete the social security paperwork and email her insurance company to secure coverage for treatment with Spinraza, a medication approved to treat the condition.

In all, the researchers interviewed 15 parents and found that they had difficulties obtaining secondary insurance based on state eligibility criteria and accessing needed healthcare services, and repeated interactions with insurance representatives. The researchers found familiar frustrations for anyone who has navigated any bureaucracy's phone system, been provided with contradictory or wrong information, and

"This report should be a call to action. We can do more to help our families, and we must."

— Marissa Penrod



Shortening the Diagnosis-to-Treatment Time for Rare Disease Patients

More than 70 percent of rare diseases are genetically determined. While next generation sequencing has made it possible to rapidly diagnose a growing number of rare diseases and a growing number of therapies are reaching the market, the move from diagnosis to treatment can pose delays as physicians may lack information needed to provide proper treatment.

The Treatabolome, a project developed under the Solve-RD European Research Project, is working to reduce treatment delays by directly linking diagnosis and treatment information through an online platform disseminating rare disease and gene-specific treatment information to health-care professionals.

“There are treatments available for an increasing number of rare diseases, but there is often a substantial delay before patients receive the right treatment,” said Gisèle Bonne of Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche

en Myologie, in Paris. “Although targeted treatments are currently only available to a minority of patients with rare diseases, recent developments point towards a steep increase in the coming years, as suggested by the development of multiple gene therapies and the steady increase in the number of orphan drug applications.”



“There are treatments available for an increasing number of rare diseases, but there is often a substantial delay before patients receive the right treatment.”

—Gisèle Bonne

The intention is that as the Treatabolome platform is finalized, the main body of data will be derived from expert-led systematic literature reviews. In an effort to feed this emerging platform, Bonne served as guest editor of a special issue of the *Journal of Neuromuscular Diseases* featuring systematic literature reviews on rare neurological

and neuromuscular disorders. The published reviews bring state-of-the-art, evidence-based information in a standardized format that is easily uploaded to the Treatabolome database.

As the Treatabolome project expands to include other rare diseases, it will call on rare diseases experts from all 24

European Reference Networks and the whole scientific community to produce other datasets to feed the database and facilitate treatment awareness for rare diseases. The project is also exploring ways to harness artificial intelligence to automate updates to the database using machine-led text mining of publications.



been told something their child needed would not be covered, even though a medical expert said it was medically necessary. While it's one thing to weave through the maze of a cellphone company or bank's phone system, one participant in the survey described doing so while suctioning a child's trachea tube while on hold.

One common theme to emerge from the study was the frustration parents felt dealing with insurance company representatives who had no understanding of the particular condition that a child had and the lack of deference to medical professionals to make the decision about what care a patient needed. In one instance, a child with SMA, whose doctor said should be on a pulse oximeter to monitor the oxygen level in her blood, was denied coverage for it several times by the insurance company. Finally, the doctor wrote for oxygen (something the child did not require and is contraindicated in SMA but was necessary to get the insurance to approve the pulse oximeter).

Rare disease patients, who often rely on a small pool of specialists, also have to overcome hurdles to access the few doctors who may be experts on their conditions or be forced to pay a higher out-of-pocket fee if they choose to see them. They must also stay on top of a wide range of matters to ensure they get the coverage to which they are entitled. In one case, a participant in the study reported that she must call a durable medical equipment company directly to ensure a claim will be submitted to her insurance company because if the company makes an auto-shipment without billing the insurance company, she would be responsible for the bill.

While the authors suggest a list of reforms to improve the landscape—this includes greater

transparency, the use of trained rare disease navigators, centralized resources on financial assistance programs, consistent mechanisms for rare patient enrollment in insurance, and consistency of coverage—the takeaway for patients may have less to do with needed reforms and more a reminder for the need for vigilance. "Individuals are often grateful for a supportive network of peers and providers to identify programs and eligibility for additional assistance, but the final responsibility falls to them," the authors write.

Patients Feel Unsupported

For rare disease patients, it is not only the time and cost of managing conditions, but the feeling that they do not receive adequate support for their psycho-social wellbeing. One study, conducted by researchers at the University Medical Center Hamburg-Eppendorf and published in the *Orphanet Journal of Rare Disease*, is the first study aimed at investigating supportive care needs in patients with different rare chronic diseases across a broad range of areas including health system and information, physical needs, patient care, sexuality, and psychological needs.¹⁸

The results were based on responses from 304 participants at least 16 years of age with 81 different rare diseases. More than 80 percent of the respondents were female. The study relied on both a quantifiable survey as well as open-ended questions. It used a survey of supportive care needs validated in cancer patients and a reference sample of cancer patients as a comparator.

In all five areas the researchers explored—health system and information, psychological needs, physical and daily living, patient care and support, and sexuality—patients with rare diseases expressed greater needs than did patients with cancer. The majority of participants reported that they do not feel sufficiently socially supported. Patients sought support from personal contacts, including partners, family members and self-help groups, rather than medical professionals. They also expressed a desire for better information on the disease for

themselves, their spouses, caregivers, and the public. They hope that better public education would allow others to better understand them and not label them as handicapped.

In addition, the study found that respondents wished they had better access to self-help and contact with other patients affected by the same condition. In particular, they wanted better information from their physicians after a diagnosis and wanted access to an online forum for the illness, or an email address or phone number of someone with the same condition. The participants also expressed the need for support in everyday life tasks and to facilitate job-related circumstances, such as flexible work hours to attend medical appointments. And they expressed the desire for greater support of their sexual needs through receiving information about sexual relationships.

The authors note that the sample does not reflect a representative picture of patients with rare diseases. It recruited participants for the study through outpatient clinics, patient organizations, and self-help groups for rare diseases. The researchers said it is likely that it reached patients who are well integrated into care structures. Patients with rare diseases for whom there are no patient associations or specialist clinics available may have even greater support needs," the researchers wrote.

A separate study from the European rare disease organization Eurodis found people with a rare disease in Europe give their healthcare experience a medium-low rating. The Rare Barometer survey produced by the organization was based on more than 3,900 submissions received through 2019-2020. Healthcare services for rare and complex conditions only occasionally consider key aspects, such as follow-up consultations and appropriate psychological and social support, the survey found. Moreover, the results show that patients living with a rare disease have a worse healthcare experience than other patients affected by chronic diseases. While both require multidisciplinary care and have broadly similar needs, patients with rare diseases seem to have a harder time accessing care that meets their needs.

Many people living with a rare disease report feeling left alone with their concerns. Orienting patients towards community support groups, alongside adequate psychological and emotional help, emerges as a key factor in ensuring a better healthcare experience. Among the three priority areas for improvement, the respondents indicated the need for follow-up consultations, more orientation on resources and support, and psychological assistance.

In order to support patients and caregivers, experts should also improve coordination with other doctors and provide recommendations to patients on how to manage the disease in their daily life, for instance by setting specific goals or developing disease management programs, the report said.

Building Frameworks, Addressing Needs

Across the globe rare disease patient organizations in 2021 took steps to create national and international frameworks for rare disease to accelerate diagnosis, raise awareness, and improve treatment.

In July 2021, Rare Diseases International, the European rare disease organization Eurodis, and the NGO Committee for Rare Diseases called on the United Nations to pass a resolution that recognizes the challenges faced by people living with a rare disease and to promote full participation and inclusion in society for all people. Brazil, Spain, and Qatar are the core group of U.N. Member States leading the call for the adoption of the U.N. General Assembly Resolution, the groups said.

"Most persons living with a rare disease around the world are at the margins of society, unrecognized, stigmatized, and discriminated. They face a lack of understanding of the multi-dimensional challenges that impact all aspects of their life, beyond just health," Durhane Wong-Rieger, president and CEO of the Canadian Organization for Rare Disorders and RDI Council Chair wrote in calling on Canadian Minister of Health Patty Hajdu

to support the call for a U.N. resolution. “They are a psychologically, socially, culturally, and economically vulnerable population, facing discrimination and specific challenges in health-care, education, employment, and leisure. The impact heavily affects families too and is detrimental to active participation in society, causing increased impoverishment and isolation.”

Health Canada, the federal department in Canada that is responsible for the country’s national health policy, in January 2021 restated its commitment to a universal pharmacare program and said it is accelerating efforts to achieve this through a rare disease strategy to help families save money on high-cost drugs. To that end, it asked Canadians, particularly rare disease patients and stakeholders, to share their views on what a national policy should include. It created an online questionnaire and encouraged citizens to review a discussion paper that laid out key considerations.

“Federal, provincial, and territorial officials are working closely to build a strategy that works for all Canadians in the context of Canada’s health system and respect the role of provinces and territories in health care delivery,” Health Canada said. To help Canadians with rare diseases access the drugs they need, the federal budget in 2019 proposed an investment of up to \$1 billion over two years, starting in 2022-23, with up to \$500 million per year ongoing.

“Canadians with rare medical conditions face many unique challenges,” said Canadian Minister of Health Patty Hajdu, “and we’re committed to improving access to the medications they need.”

In Europe, Eurodis in February 2021 issued a call for a new European policy framework for rare diseases with its Rare 2030 Recommendations. The recommendations, based on suggestions from more than 250 experts, are

Creating Standards of Care

Takeda Pharmaceutical partnered with the Washington, D.C.-based hospital Children’s National to launch a first-of-its-kind rare disease clinical protocol program that will provide a networked system for the development, dissemination, and curation of protocols to help standardize the process of diagnosis and care for patients with rare diseases.



“The Takeda commitment will help harness technology to revolutionize access to care standards for rare disease.”

—Marshall Summar

Rare Disease Clinical Activity Protocols (Rare-CAP) will be led by the Rare Disease Institute at the new Children’s National Research & Innovation Campus that opened in February 2021 on the grounds of the former Walter Reed Army Medical Center. Takeda is committing \$3.9 million over five years to help launch and sustain the program.

Rare-CAP will leverage several novel features to serve as a protocol platform that reduces barriers for researchers, clinicians, and patients in determining appropriate diagnosis and clinical care for rare

disease patients. This includes ongoing input from patients and families and an open “wiki” format for near real-time updates from vetted contributors to enable access to the latest, real-world data.

“Just as Wikipedia revolutionized how we think of the encyclopedia,” said Marshall Summar, founding director of the Children’s National Rare Disease Institute and chief of the Division of Genetics and Metabolism at the hospital, “the Takeda commitment will help harness technology to revolutionize access to care standards for rare disease.”



intended to provide an EU roadmap for 2030 across diagnosis, treatment, research, data, and integrated care.

Despite the progress that's been made in Europe, the organization said people living in Europe still face an average of four years to get a diagnosis. Only 6 percent of the population living with a rare disease has access to a treatment for their condition. And more than half (52 percent) of patients and caregivers report that their condition has a severe or very severe impact on their daily lives. A new European policy framework, they said, would provide concerted strategy across different areas, guide the implementation of national plans for rare diseases with the same measurable objectives, and encourage continued investment in rare diseases.

"It is time to reset Europe's rare disease focus for the next decade: we need a policy framework in Europe adapted to today's realities, to embed excellence and bring policies in line with new technologies, values, and infrastructures," said Yann Le Cam, CEO of Eurodis. "Europe's efforts since 2009 have shown how much progress can be made when national plans and strategies for rare diseases are coordinated across countries and integrated at EU level. We cannot lose momentum now."

The Rare 2030 Recommendations offer a roadmap for a new rare disease framework by establishing measurable goals for the first time. In line with the UN Sustainable Development Goals, such goals set a common direction for all EU Member States to make tangible change for all their citizens living with a rare disease. The hope is that if implemented, by 2030 the average time to diagnosis will shorten to six months of coming to medical attention, 1,000 new therapies will be approved and be three to five times more affordable; and the social, economic, and psychological vulnerability of people with rare disease will be reduced.

Among the recommendations are more consistent use of harmonized standards and programs across Europe for faster and more accurate diagnosis. It calls for the prioritization of rare disease research across basic, clinical,

translational, and social research. It also seeks a highly specialized healthcare ecosystem, with political, financial, and technical support at European and national levels that leaves no person living with a rare disease uncertain about their diagnosis, care, or treatment. And it calls for the creation of a culture encouraging meaningful participation, engagement, and leadership for people living with a rare disease in both the public and private sectors.

In the United Kingdom, the U.K. Department of Health and Social Care in January 2021 released the U.K. Rare Diseases Framework intended to provide a national vision for how to improve the lives of people living with rare diseases.¹⁹ The framework is intended to build on the commitments the government made in the U.K. Strategy for Rare Diseases released in 2020 with the goal of making positive changes in how people in the U.K. diagnose, treat, and care for patients with a rare disease.

The framework, which emerged from the U.K.'s National Conversation on Rare Diseases helped identify four key priority areas to bring about real change for patients. This includes building upon recent advances in diagnostic technologies through genomics and data analysis to help patients receive a final diagnosis faster and reduce the diagnostic odyssey. The framework calls for efforts to increase awareness of rare diseases among healthcare professionals while ensuring that those involved in patient care are provided with the appropriate education and support to improve the quality of care. It also calls for the removal of unnecessary barriers to improve the coordination of care throughout the patient journey. Finally, it seeks to use new technology and digital tools to build on the U.K.'s research and life sciences to improve access to innovative treatments and specialist care. To facilitate effective implementation of these priorities across the U.K., England, Scotland, Wales, and Northern Ireland will each develop and publish a plan detailing the steps they will take to meet the framework aims in a way best suited for their population and health system.

Other European countries also took steps to invest in the diagnosis and treatment of people

"We need a policy framework in Europe adapted to today's realities."

—Yann Le Cam



“Our goal is to put South Africa on par with other countries such as the EU, U.K. and BRICS, by having a National Rare Disease Policy.”

—Kelly du Plessis



with rare diseases. *The First News* in Poland reported in March 2021 that the Polish government would spend \$175 million (PLN 700 million) over two years to improve the care of people with rare diseases as part of the nation's Rare Disease plan. Poland has an estimated 2 million to 3 million people living with a rare disease. While the Rare Disease Plan features 40 specific tasks with deadlines, the initial effort will focus on establishing a center of expertise in Poland to minimize the travel patients need to undertake to access specialized care. Other parts of the plan include the creation of a national registry of rare disease, a program to improve access to medicines and medicinal foods, and the development of infrastructure and methodology for the diagnosis of rare disease.²⁰

Beyond Europe

The Australian Government, to support the approximately 2 million Australians living with a rare disease, raise awareness, and create new educational programs, awarded \$3.3 million in funding. The funding will drive the development and delivery of awareness and educational resources, as well as care and support services, for people living with a rare disease, their families and caregivers, health professionals, and the wider population. The funding follows the nation's first nationally coordinated effort to address rare diseases with the release of the National Strategic Action Plan for Rare Diseases in February 2020.

Separately, the Australian government provided a \$1.4 million (AUD 1.9 million) grant to the University of New South Wales to deliver the Rare Disease Awareness, Education, Support and Training Project (RArEST). This project will develop and deliver rare disease resources, education, and training that will include a focus on mental health, and social and emotional well-being. Rare Voices Australia received \$742,300 (AUD 1 million) for its Rare Awareness Rare Education Project (RARE Project). The project will develop and deliver rare disease awareness, information, and education activities including a national rare disease digital platform. This digital platform will provide specific information on

how to access rare disease expertise, support, and services in the health and disability systems, and elsewhere. Other grants include \$146,980 (AUD 198,000) over two years to the Australian National University for work to enhance health-care provider awareness to improve the diagnosis of rare diseases. It also included a \$137,330 (AUD 185,000) grant to the National Childhood Dementia Awareness, Support, and Education Project to develop and deliver awareness, information, and education for families and health professionals about childhood dementia.

At the end of 2020, Rare Diseases Access Initiative, a coalition of patients, industry, and payers, and the patient organization Rare Disease South Africa called for the establishment of a national framework for rare diseases in South Africa to “ensure the most equitable, effective, efficient, and coordinated approach to rare diseases.”²¹ They said a National Rare Disease Framework for South Africa will ensure effective rare disease policy to transform patients' lives and prevent South Africa from falling behind other countries.

“Our goal is to put South Africa on par with other countries such as the EU, U.K. and BRICS, by having a National Rare Disease Policy,” said Kelly du Plessis, CEO and Founder of Rare Diseases South Africa. “Participants concurred that without a rare disease framework and policy, South Africa is falling behind other countries and our chance of achieving universal healthcare is diminished,” she concluded.²²

Cost a Common Theme

One common theme from country to country is developing plans for how to pay for the cost of rare disease drugs. In Singapore, where there are more than 2,000 patients estimated to be living with rare conditions, the government launched The Rare Diseases Fund in 2019 to provide financial assistance for the cost of treatment of a rare condition. The fund provides a matching grant of \$4.05 (S\$3) for every \$1.35 (S\$1) in public donations to the fund. However, it covers patients with just four rare diseases (primary bile acid synthesis disorder, Gaucher disease type 1 or type 3, hyperphenylalaninemia

due to tetrahydrobiopterin (BH4) deficiency and Pompe's disease). Only eight patients have sought funding through the program, seven of whom received support.

Member of Parliament Cheryl Chan called for expanded support for patients with rare conditions, the Singapore publication *Today* reported. She'd like to see the diseases and the eligible drugs expanded so more people could benefit from the program.²³ Senior Minister of State for Health Koh Poh Koon told *Today* the government is looking to expand the program to including three more diseases and five more medicines for eligibility, but doing so would be difficult without more donations.

In one of the more controversial approaches, India's solution has been to turn to crowdfunding as a way to address the need for access and affordability for medical care for costly rare diseases. India's National Policy for Rare Diseases 2021 included a policy that provides for crowdfunding as a way to bridge the gap between the cost for rare disease treatments and what the government will pay. The finalized policy said it will be difficult for the government to fully finance the treatment of high-cost rare diseases, according to a report in the *Hindustan Times*.²⁴ "The gap can, however, be filled by creating a digital platform for bringing together notified hospitals where such patients are receiving treatment or come for treatment, on the one hand, and prospective individual or corporate donors willing to support treatment of such patients," the policy said.

In August 2021, the India government took live its crowdfunding portal for the treatment of rare disease patients. Under the plan, eight hospitals designated as Centers of Excellence that provide treatments to rare disease patients can provide information through the portal about a patient's treatment and the cost of care. Corporate and individual donors are invited to contribute.

The Organization for Rare Diseases, prior to the final release of the revised National Policy for Rare Diseases 2021, said that the government has taken a "cavalier approach" by suggesting patients who are ailing, or their families, should rely on crowdfunding for treatment. "Picture the scene: a person desperately in need of medical intervention or continued medicines, must themselves or with help from their family organize fundraisers so that they may continue living," the organization said. "A stark picture indeed, one that amplifies either the fact that the struggles of the rare disease community don't matter, or worse, that the government doesn't believe it has a role to play in ensuring holistic, affordable care for all rare diseases."²⁵

Though a national policy based on crowdfunding may seem shocking to some, in the United States, it is a reality for many. The crowdfunding site Gofundme calls itself the leader in online medical fundraising. Though by no means limited to rare disease, the sites said it hosts more than 250,000 medical fundraisers a year that raise more than \$650 million annually.²⁶ ■



Endword

If a Gene Therapy Is Created, Does it Cure a Patient?

We are in a time of accelerating advances in science and technology that promise to radically alter how physicians diagnose people with rare diseases and treat them for these conditions. It is not difficult to imagine a world where doctors will be able to diagnose and cure someone with a rare condition prior to birth.

Artificial intelligence is already becoming a standard tool for drug developers and an essential component in interpreting the large data output of whole genome sequences. Scientists are harnessing it to identify potential therapies to repurpose as a treatment for individual patients and it will likely play an increasingly significant role not only in the diagnosis of patients, but also in helping doctors determine the best case for treatment in the clinic. It may be that through machine learning, doctors will know when the sound of hoofbeats warrant thinking zebra.

It is easy to be enamored with what is possible, but it is essential to consider the obstacles that remain in place to end the suffering caused by rare diseases, as well as address the immediate needs that patients, caregivers, and families face. For people with rare diseases, biomedical advances can't move at a fast enough pace in the face of the experience of loss to progressive illness. While it is important to drive toward a vision of the future to make it a reality, it is also essential that we recognize, understand, and address the reality that rare disease patients face today.

Funding the development of a therapy that could correct a misspelling in a gene and cure a patient of a rare, genetic

disease provides hope for a better future. But for many rare disease patients and their families, their thoughts, by necessity, are often focused on more mundane challenges. This might include things like locating a doctor who is familiar with their condition, fighting with insurers over coverage to which they are entitled; and finding ways to pay for the supplements, equipment, and care their insurance does not cover.

Tapping the Advocate Within

At Global Genes, we are fortunate to know many extraordinary advocates who have given themselves to funding research, driving the development of potential cures, and working for policies that would benefit all rare disease patients. In the face of tragic loss, we have witnessed the endless fight these advocates pursue, even if they and their loved ones won't benefit from their work.

As a greater emphasis today is being placed on equity, diversity, and inclusion, it is worth remembering that rare diseases affect people of not only different racial and ethnic backgrounds, but also that it doesn't distinguish based on education, economic status, or geography. While half of the people affected by rare diseases are children, there are many adults who struggle with rare diseases as well and face a set of complex challenges.

Many advocates who come into the public eye, found organizations, and take on leadership roles in the community are educated, successful, and financially well-



off. Many other members of this community find themselves too consumed with managing their condition or the condition of their loved one while trying to eke out a living to give themselves over to advocacy. They may not have much in the way of support from family members or spouses. And the tasks of getting through a day, one day at a time, may be so consuming as to leave them little time for anything else. It is a diverse community.

Though not everyone is able to start foundations, craft research agendas, and raise millions of dollars to fund research, and there is much that rare disease patients and their loved ones cannot control about their conditions, patients or caregivers are not powerless to help themselves and help others. There are simple things that people within the rare disease community can do. For patients or caregivers looking to contribute to advance an understanding of their disease, develop treatments and cures, and advance the cause of people with rare diseases, there are simple things they can do to without having to devote significant time and effort.

Understand the common fight: All too often, members of the rare disease community view the quest for funding, research, and treatments as a zero-sum game. Not only can

there be competition between groups advocating for different conditions, but people, often advocating for the same condition, work at cross-purposes. They may also have different views on the best way to advance their cause. Work to find common ground.

Help others learn from your experience: Everyday there are people who are presented with a diagnosis of a rare disease. No one understands the challenges they will face and the obstacles ahead better than someone who is further along the journey. It is likely that in the past someone offered them the perspective and counsel that only someone who had gone through the experience could provide. When the opportunities come, pay it forward.

Engage in everyday advocacy: In everyday life teachable moments present themselves to make others aware of what a rare disease is and what it is like to live with one. Many people may not want to advertise their illness or call attention to it. But when opportunities arise, use them to help eliminate ignorance, increase awareness, and foster compassion.

Teach the experts: Don't underestimate the value of your experience and understanding of a rare disease condition. Insights into the daily

experience with a condition makes patients and their caregivers the expert on their own disease. Share your insights with doctors, researchers, and drug developers when the opportunity arises and don't be afraid to offer contrary takes on statements they may make.

Share your data: Data is essential to understanding a rare disease, accelerating the time it takes to diagnose a condition, and developing treatments. The very nature of rare disease, though, make this a critical element that is in short supply. The lack of data makes it difficult to entice drug developers to pursue treatments and cures. A new generation of data platforms is enabling rare disease patients to contribute their data and share it with researchers and drug developers. Make sure you understand who has control of the data and who determines who can have access to the data. Several of these new platforms leave that power with the patient.

Innovate Everywhere

While a rare disease patient or their loved ones may feel that no cost is too great for a cure, governments and payers do not share that belief. They not only view healthcare as a finite source, but that paying for one patient takes from another. They must make decisions to allocate resources across a population. Consider the COVID-19 vaccine, for which

governments have paid between \$2 and \$20 a dose. As a growing number of potentially curative therapies advance toward the market, the cost of treating a rare disease and questions of who will pay and how much will become an increasing point of contention. Ben Franklin said an ounce of prevention is worth a pound of cure, but how will a government weigh 100,000 or 1 million doses of a vaccine to a gene therapy for a single patient?

New business models are emerging that seek to address that, but business models and efforts like precompetitive alliances to reduce the cost of developing and manufacturing genetic medicines will not be enough. Knowing how to make and design a therapy that can deliver a cure to someone with a rare disease does no good if affordability prevents access.

As organizations place greater attention on issues of equity, diversity, and inclusion, it will be important to remember that rare diseases do not discriminate on the basis of geography or economics. These conditions affect a global population. While innovation is driving us toward new ways to treat and potentially cure rare diseases, efforts will be needed not only to develop these medicines, but to deliver them in affordable ways.

Innovation shouldn't be the problem. It should be the solution. ■



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Credits and Acknowledgments

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