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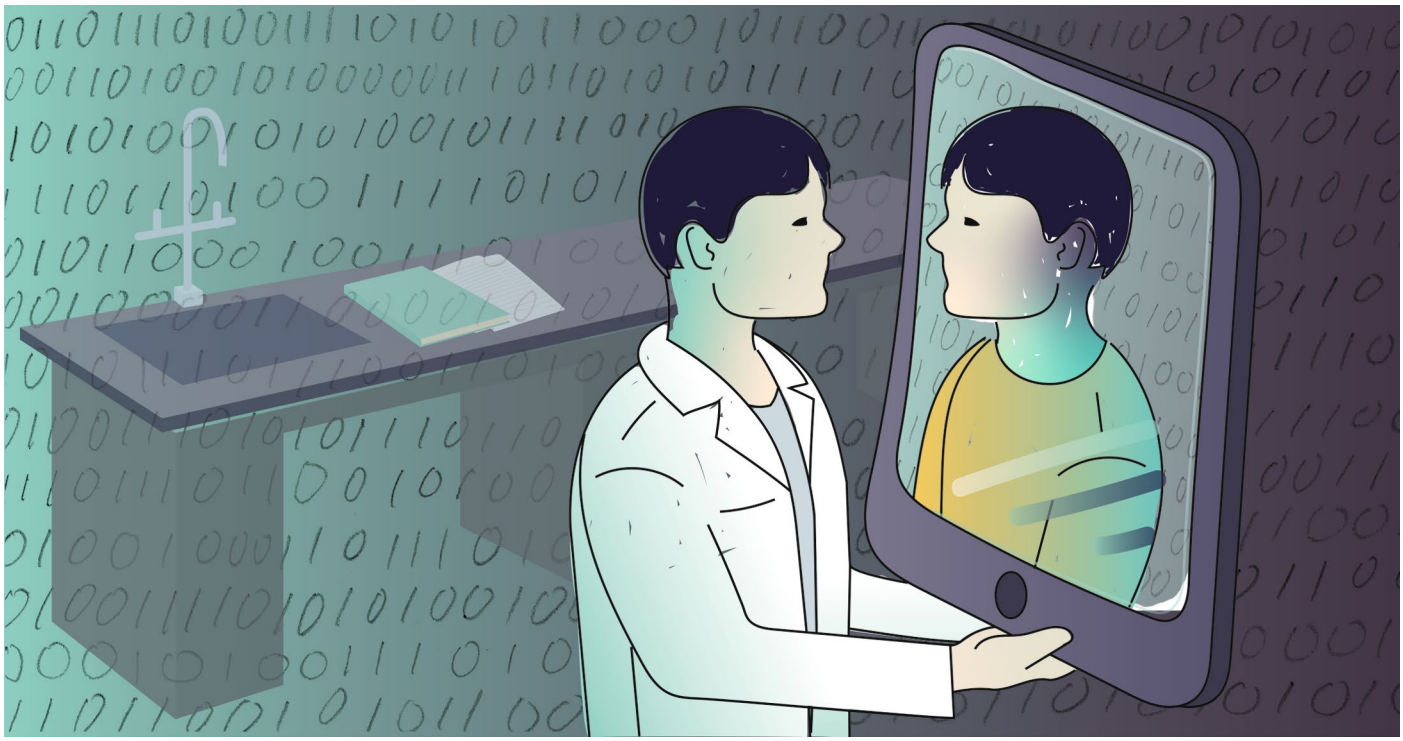


Credit: Erin Dewalt

Their lives in their hands

The devastating diagnosis of a rare disease is prompting an increasing number of people to go to the bench and take research into their own hands

Malorye Allison Branca

Corrie Painter was a wife, a mother and about to get her PhD in biochemistry in 2010 at the University of Massachusetts Medical School when she found a lump in her breast. It turned out to be more complicated to diagnose than most lumps, and it was several months and several biopsies later before she got the shattering diagnosis of a grade 3 angiosarcoma. This is an incurable disease, she was told; most patients live fewer than five years. What's more, only a few hundred people are diagnosed with the condition every year in the United States, so it's not on the radar of drug developers. Painter's next thought was, "OK, now what do I do?

Painter's journey is unusual in some ways, but also mirrors a growing trend among people diagnosed with rare conditions: patients become not only active disease advocates but also active researchers. Building on what is now a long history of 'do-it-yourself' patient advocacy[1], some are making remarkable strides advancing research in rare conditions. They are also helping develop and pass along a 'blueprint' for others seeking cures for conditions long neglected by the mainstream biopharmaceutical industry.

Do it yourself

Painter ended up cofounding the nonprofit Angiosarcoma Awareness, raising several hundred thousand dollars to start (and every year since), and then worked on convincing scientists to research her disease, in particular to follow an intriguing lead she unearthed. Digging through an old list server archive called the 'Association of Cancer Online Resources', Painter found a contact who provided her notes from William Coley, who is sometimes referred to as "the father of immunotherapy" for work he did in the late 1800s. Painter says those notes revealed that five patients with angiosarcoma whom Coley treated with his version of immunotherapy—a killed bacterial vaccine—went into remission, at least temporarily. That glimmer of hope was enough to inspire Painter, who went to work herself to explore tumor progression in zebrafish, which provide a remarkable platform for visualizing development[2].

Today, through a mixture of medical care, knowledge, grit, technological advances and some luck, Painter has finished her PhD and is now directing a high-profile project that gives patients a role in advancing research into their 'own' diseases. The Broad Institute's Count Me In program (https://www.mbcproject.org/about) is creating sharable databases of tumor samples and patient medical records and encouraging researchers to partner directly with patients.

Her Broad team's first project was to create a database for metastatic breast cancers that now has information from more than 5,400 patients. When her boss, Broad president and founding director

Eric Lander, asked what database they should launch next, Painter sheepishly asked "Angiosarcoma?" Lander thought for a moment and then enthusiastically said, "Yes! That's exactly what we will do next."

Now Count Me In's Angiosarcoma Project comprises data from more than 450 patients. Painter and her colleagues have even more databases in the works, and research findings are already being generated. "We released the first data from breast cancer in 2017, and more than a dozen research papers have been published on this data," she says. A 2019 tour-de-force study of angiosarcomas in 74 dogs showed that the cancer shares genes and pathways in dogs and humans, opening up a potential large-animal model, which is sorely needed given the small human patient population[3].

Role models

Over the years, many people, among them some scientists, have taken a stab at do-it-yourself drug discovery. Most have been quickly cowed by the difficulty, complexity and enormous resources needed to successfully accomplish such an endeavor. However, two women are credited with succeeding at this seemingly impossible task: Sharon Terry, president and CEO of the Genetic Alliance, and Kathy Giusti, founder of the Multiple Myeloma Research Foundation.

A former chaplain and stay-at-home mom, Terry essentially turned herself into, if not an actual scientist, at least a very good facsimile of one after her two young children were diagnosed with a rare and incurable disease in 1994. She helped sequence the gene (*ABCC6*, encoding a transporter protein) underlying that disease[4]—pseudoxanthoma elasticum, or PXE, which causes mineralization of connective tissue, leading to blindness and hardening of the arteries—and was named as an inventor on the gene's patent. Since starting her odyssey, Terry has authored or collaborated on more than 150 scientific publications, of which 30 are clinical PXE studies.

As CEO of the Genetic Alliance, an advocacy group for genetic diseases, she has also overseen the creation and sharing of numerous critical tools that can help these groups gather data about their diseases. Providing such data can help 'de-risk' a rare disease and make it more attractive to pharmaceutical companies. The Genetic Alliance has more than 10,000 members from advocacy, research and healthcare organizations. Its tools facilitate building biobanks, collecting health data directly from patients and doing other things that can help advocacy groups accelerate their progress.

Box 1 | The gold standard

Most patient advocacy groups, whether they comprise one person or hundreds, dream of having unfettered access to a pharmaceutical company dedicated to their disease. But only one organization has come close to doing it—the Cystic Fibrosis Foundation (CF Foundation).

"People look at the CF Foundation as the gold standard. They raised the funds, and built the infrastructure to try and meet all of their patients' needs," says Katherine Beaverson, senior director and patient advocacy lead of the Rare Disease Research Unit at Pfizer. The foundation's groundbreaking deal with high-throughput screening pioneer Aurora Biosciences turned into a longstanding relationship with Vertex Pharmaceuticals (which acquired Aurora in 2001). That partnership has changed the horizon for a growing number of people with cystic fibrosis, while fueling the growth and expansion of Vertex, which was the first company to develop drugs that address the underlying cause of cystic fibrosis.

There were a few remarkable features to the program that Robert Beale, the CF Foundation's former president and CEO, undertook starting in the mid-1970s. That started with an investment in basic research and then extended to funding in companies, starting in the 1990s. "Bob made two observations," says Mike Boyle, current senior vice president of therapeutics development at the CF Foundation. "He saw that all scientific discoveries were not being translated into new therapies, and that most of the breakthrough science was not being applied to cystic fibrosis."

These realizations translated into a vision and was fueled, in part, by more than $150 million raised by Joe O'Donnell, the father of a child who died of cystic fibrosis at age 12. O'Donnell is a successful businessman who decided to throw his weight against cystic fibrosis, even when it was too late to save his own son .

The science was theoretically straightforward. Cystic fibrosis is caused by a myriad of known mutations in the gene that produces cystic fibrosis transmembrane conductance regulator (CFTR), a protein that channels chloride ions out of cells lining the body's inner surfaces. The drug developers identified those mutations and designed drugs to target them. Beside finding the targets and designing the drugs, one of the main complications was that there are so many mutations that cause the disease. But none of that has kept Vertex from launching multiple drugs, each of which address the underlying cause rather than merely the symptoms of cystic fibrosis.

Today, the results of CF Foundation's relationship with Vertex is envied by many disease foundations and illustrates the huge advances such a partnership can bring to both the science and the business aspects of rare-disease research. There are more than 50 trials in cystic fibrosis ongoing in the foundation's network at any one time, with >90 academic research centers involved and 37 companies. Ten drugs have been approved for CF (including three CFTR modulators from Vertex). All of these were made possible thanks in part to funding from the foundation.

"We're not done yet," says Boyle. "We want treatments for all the underlying causes and effects of this disease."
But he also recognizes how far they have come. "This model has transformed cystic fibrosis, and while it is going to be very hard for anyone else to follow it, I believe that can be done."

Giusti, meanwhile, had unique insider information from the drug industry when a cancer diagnosis forced her to rethink her life, leave her job and launch her own research effort. In 1996, she was at the peak of a successful career in industry and was director of the worldwide arthritis franchise at Searle, one of the largest pharmaceutical companies at that time, when she was diagnosed with multiple myeloma, a rare and difficult-to-treat blood cancer.
She began her fight against the disease better informed than most about what lay ahead. After learning as much as she could about the malignancy, she set out to draw up a strategic plan, raise funding and attract scientists to the multiple myeloma field.

Since then, Giusti has put in place a system to transform the number of patient samples collected. She has attracted donors and scientists to the cause. Her foundation has helped advance more than 80 phase 1 and 2 trials in the cancer, helped bring 11 new drugs to the clinic. During this time, the average lifespan of a patient with multiple myeloma has tripled. A Harvard Business School case study that outlines her approach

begins with a quote from Eric Lander: "This is the model for cancer. It is the model for medicine; of what we have to do"[5].

Building foundations

Terry and Giusti, and trailblazers like them (see Box 1), have been an inspiration to people facing the shock of a dire diagnosis. "Sharon and Kathy were invaluable to me," says Josh Sommer, the co-founder and executive director of the Chordoma Foundation, who has likewise produced a trove of research findings on his disease.

"Getting help from them, I felt like I was standing on the shoulders of giants," says Sommer, who was an undergraduate studying engineering at Duke University when he was diagnosed with a chordoma at the base of his skull. "If it were not for them, and several others, we could never have come this far."

Chordoma is a rare and deadly type of cancer of the spinal cord. At the time Sommer's disease was diagnosed in 2006, Michael Kelley's lab at Duke University Medical Center happened to be the only US National Institutes of Health (NIH)-funded group in the country focusing on the cancer, so Sommer began his research journey there. He has since, in 2007, established his own foundation, through which he has dramatically increased the amount of available funding and number of clinical trials for his disease. He left his career as a scientist, but has led his foundation and helped establish a biobank with more than 20 cell lines, and numerous animal models, while recruiting investigators for trials and sponsoring research published in more than 50 peer-reviewed articles. Sommer's foundation is actively seeking to promote the application of innovative approaches and technologies to chordoma, funding Craig Crews at Yale to work on drug-discovery approaches for targeting brachyury protein, which is expressed in the malignancy and thought to contribute to pathogenesis, to the proteasome for degradation; Daniel Nomura at University of California, Berkeley, to work on the use of chemoproteomic platforms to discover brachyury binders; and Opher Gileadi of Oxford University, David Drewry of University of North Carolina, Chapel Hill, and Charles Lin at Baylor to do fragment-based drug discovery of brachyury inhibitors.

David Fajgenbaum, who has an MD, an MBA and an MSc, has also created a roadmap for attacking rare diseases like his own, Castleman's disease, which covers a group of uncommon lymphoproliferative disorders. The disease struck the former vibrant athlete suddenly, while he was a third-year medical student, and brought him close to death five times.

Like many patient advocates, Fajgenbaum has done everything from raising funds to sponsoring research and spreading awareness. In his recently released book, *Chasing My Cure*[6], Fajgenbaum demonstrates his passion for helping others follow his lead. "I had no idea what I was doing when I started out," he says. After uncovering a drug he thought could be repurposed for his disease (sirolimus, a small-molecule mTOR inhibitor), he began testiing that drug on himself. He is currently symptom free and overseeing more than a dozen research projects at the Castleman Disease Program he directs at the Perelman School of Medicine at the University of Pennsylvania. "Anyone in this situation should know that no matter what their background is, they can make a difference that may be able to save their own life. The tools are there now," he says.

Although their stories are each unique in some ways, these pioneers and their shared experiences are informing others who have received a devastating diagnosis about the best way to use science and fundraising and organize to tackle it.

Network, network

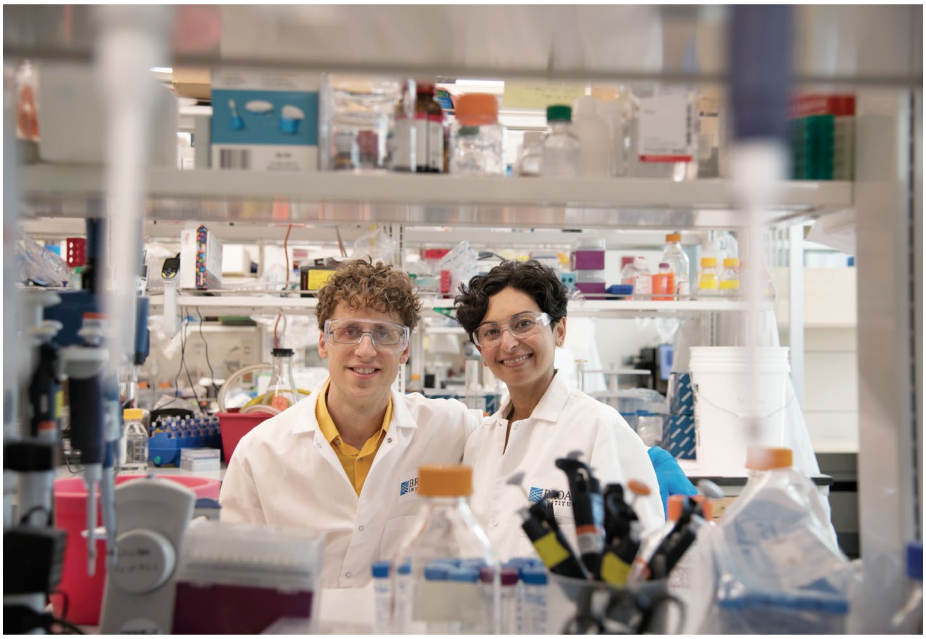
Not everyone actively researching their own disease establishes a foundation, of course. But they are finding many ways to contribute to the advance of knowledge. One example is Monkol Lek, a former software engineer in Australia, whose life took a radically different direction when he started losing mobility as a result of limb-girdle muscular dystrophy. After joining a human genetics group at the University of Sydney Australia, he had a serendipitous meeting with the Broad's Daniel MacArthur. MacArthur subsequently brought him over to the Broad as a postdoc, and Lek took part in large-scale human genomics studies, culminating in the creation of a database of genetic variants from 60,000 people (ExAC), a highly valued resource in the human genetics community[7]. Now running his own lab at Yale University, Lek is not restricting his research to his own condition. "The muscle is very complex," he explains, "and by studying one [disease] we will learn about more of these similar conditions." Lek is a member of Cure Rare Disease (CRD), a consortium whose founder, Rich Horgan, created it in part because Duchenne muscular dystrophy runs in his family. CRD encourages the development of treatments for a range of rare conditions. Currently, Lek is editing genes in mice with CRISPR to try and establish the safety and efficacy of that approach

Sufferers like Lek who are also scientifically trained have an advantage over sufferers with no training. They may, for example, spot important links or gaps in the type or amount of data available on a disease. They are also more aware of the importance of networking and recruiting other experts to study their disease. During the early phase of her journey, Painter remembers thinking that traditional path for drug discovery was not going to work for a disease such as hers: "Nobody is going to make a career out of a disease that affects 300 people a year." The foundation she formed "did everything by networking right out of the gate," she says. This was one reason she went back to defend her thesis and complete her PhD, despite still not knowing whether she would survive: it provided a way to raise her profile among her peer scientists.

Tracy Dixon-Salazar had only a high-school education at the time her daughter Savannah's epilepsy started. Her life from that point demonstrates how much one person can accomplish. Dixon-Salazar went to college and then obtained a PhD in neuroscience at the University of California, San Diego. Ultimately she went on to study her own daughter's genome in the lab of her mentor, neurologist Joseph Gleeson. Savannah's form of epilepsy, Lennox-Gastaut syndrome (LGS), is extremely severe, and the condition was affecting not just her quality of life, but also her development. "But here we were, trying one drug after another until we had tried about 30, and it was just like throwing a dart at a board," Dixon-Salazar remembers.

Then the project took a different turn; a decision was made to sequence Savannah's genome. This came about when her mentor happened to ask her, "How's your daughter doing?" Subsequently, exome sequencing revealed that Savannah's genome had 300 rare and unique variants in coding regions,

Savannah Dixon-Salazar and her mom, Tracy, reunite with Dr. Joseph Gleeson, who determined Savannah's treatment on the basis of her genetic mutations. Credit: Tracy Dixon-Salazar



Dynamic duo: faced with the knowledge that she harbors a deadly prion mutation, Sonia Vallabh and her husband Eric Minikel have changed careers and are revolutionizing how clinical development in prions is done. Credit: Maria Nemchuk, Broad Institute of MIT and Harvard

of which more than two dozen encoded proteins in calcium-signaling pathways, the majority in calcium-channel genes. This prompted a new search focusing on a series of calcium-channel blockers. Ultimately, they found one, verapamil, that reduced the number of Savannah's seizures by over 90% (ref. [8]). Dixon now serves as director of research and strategy at the LGS Foundation

Being aware of all the state-of-the-art tools and technologies that can be brought to bear in a drug-discovery project can be enabling. In 1998, when Leslie Gordon, a clinical researcher with an MD and a PhD in neuroimmunology, and her physician-husband Scott Berns discovered that their son Sam had Hutchinson-Gilford progeria syndrome (HGPS), they also realized there were few resources or options for children like Sam. HGPS is an ultra-rare disease, affecting only about 350–400 children worldwide at any time. After founding The Progeria Research Foundation, they built up the group's resources. "I knew we would need cell and tissue banks and with so few children affected by this disease, it was critical to start as soon as possible," Gordon says. The group also extended their reach around the world to include more patients in their sample bank. "At the time Sam was diagnosed, there were about one to two progeria patients diagnosed per year," Gordon says, "There are now 10–20 being diagnosed each year." This is due in large part to greater awareness worldwide, thanks to outreach, and better diagnostics.

But perhaps the most important step forward for the young foundation was recruiting the help of now-NIH-director Francis Collins to try to uncover the mutation at the root of this condition. They succeeded, as described in a 2003 publication[9]. "Our initial hypothesis was that it was an inherited recessive gene, but it turned out to be de novo in each of the samples we tested," says Maria Eriksson, who led the team. Once they discovered the affected gene, lamin A, the next step was researching and repurposing drugs to find one that acts on that gene product and has therapeutic benefit. One drug, lonafarnib, a farnesyltransferase inhibitor with anticancer activity, was chosen as it was known to have acceptable side effects in children. A study group led by Gordon took lonafarnib into the clinic and tested it in 258 children with HGPS. After 2.2 years of follow-up, children receiving the drug had a lower mortality rate[10]. Although great progress was made as Sam battled his condition, he died in 2014 from the illness, at the age of 17. Sam's personality and bravery in facing the condition were an inspiration to all those around him. "I can tell you that there is nothing like working on science and actually meeting the people you are trying to help," says Eriksson. "It is incredibly motivating."

Beyond foundations to new models

In 2010, Sonia Vallabh watched her 52-year-old mother literally lose her mind to what she was to learn was a genetic prion disease, which strikes without warning and leads to a precipitous decline and demise. Sonia received further devastating news—that she had inherited her mother's *PRNP* D178N mutation, which is an autosomal dominant mutation in the prion protein (*PRNP*) gene. That set Sonia and her husband of two years, Eric Minikel, on a completely different path from where they had been headed; Vallabh had a law degree and was working as a consultant, Minikel was a transportation planner. While still working, the couple found out all they could about prion diseases, set up a foundation to generate funding for more research into what was then an understudied disease, and ultimately decided to take matters into their own hands and leave their day jobs to do research themselves at the Broad Institute in Cambridge, Massachusetts. A few years later, the couple has a daughter (they used preimplantation genetic diagnosis to select an embryo that lacked the mutation), both have earned PhDs and they are collaborating with the pharmaceutical company Ionis to develop an antisense oligonucleotide to lower the abundance of the disease-causing protein.

Their journey to that point was not without setbacks or disappointments. The first drug lead that the couple helped crowdfund—a small-molecule drug to inhibit prion replication in mice—didn't pan out. But the couple soldiered on, deriving insight and inspiration from neuroscientist Jeff Carroll at Western Washington University in Bellingham, who had taken on an equally daunting task in Huntington's disease.

A recent publication reporting the couple's work with antisense oligonucleotides (ASOs) in a mouse prion model is encouraging[11]. Two ASOs (2′,4′-constrained 2′-*O*-methoxyethyl and 2′,4′-constrained 2′-*O*-ethyl oligonucleotides) directed against the 3′ untranslated portion and intron 2 of the mouse *Prnp* gene delivered into the brain of prion-infected wild-type mice not only reduced the production of PrP^{Sc}, the misfolded form of the prion protein, but also delayed the onset of symptoms as much as twofold when delivered early after infection. They are continuing to work on a larger package of preclinical data, which they believe will provide an important underpinning to their clinical strategy.

Moving into human testing presents challenges when working on a rare disease with no early symptoms, especially with

Box 2 | Bedside cures?

One dream that has become a reality for one family is a made-to-order treatment for a child with Batten's disease, a rare neurodegenerative disorder. In the fall of 2018, when the mutation causing the symptoms of a six-year-old child, Mila, was discovered through rapid sequencing, Timothy Yu, a doctor at Boston Children's Hospital, turned to a tailor-made, bedside application of an antisense oligonucleotide. From sequencing to delivery of the therapy to Mila, the whole process took less than a year. Given the relentless march of Batten's—which is fatal, like many other rare diseases—for Mila, every day counts.

According to Yu, the oligonucleotide designed to correct Mila's mutation was unique[14]. "In a way, this is more like a bone marrow transplant or a surgery than a pill," Yu told *STAT News*. Nine months later, her doctors reported being "hopeful" about Mila's prognosis, although they noted that she may already have experienced substantial effects from the disease.

Advocates for other conditions are hopeful that this process can be replicated. Companies such as Ionis Pharmaceuticals and Q-State Bioscience are involved in discussions with individuals and advocacy groups who are interested in taking this path.

One person hoping to see that approach succeed is Jeffrey Carroll, a neuroscientist at Western Washington University in Bellingham. Carroll began studying neuroscience shortly after receiving the news that he has the gene variant for Huntington's disease, an autosomal-dominant genetic disease. It hasn't been an easy road. "When I first started going to meetings with drug companies, and they were telling me 'Drug development in neuro is hard,' I went through what I call the valley of despondency," says Carroll. "But the rise of oligos made me much more optimistic." Carroll has been collaborating with Ionis on mouse studies of antisense oligonucleotides (ASOs) targeting the huntingtin gene for the past 10 years. Recently a study was published describing results of a safety study with a huntingtin-lowering ASO[15]. This is the first study of a drug targeting the root cause of Huntington's disease. The ASO drug appears to be safe when delivered to the spinal fluid of patients with HD[15].

Others are pinning their hopes on gene therapy. Annabel Frost's parents jumped straight into gene therapy when they determined that their daughter was suffering from a devastating and ultra-rare disease called alternating hemiplegia of childhood. Her father, Simon, isn't a scientist, but has been studying her disease and placed an ad on the freelancer site Upwork for a scientist to help research her disease. Former NIH researcher and consultant Natalia Morsci responded, and has been collaborating with Frost ever since to try and find treatment options for Annabel[16].

After several months, and meetings with other scientists, Frost and Morsci began focusing on gene therapy using adeno-associated virus (AAV) vectors. According to a *Washington Post* account, Frost is now contracting and collaborating with about 20 doctors and researchers to move this project forward. If successful, this will certainly be another inspiration for desperate patients and family members[16].

prion disease, where treatment appears to be most effective before any outward sign of the disease manifests. The couple are currently developing a strategy for testing prion-protein-lowering ASOs in presymptomatic people bearing a prion mutation, which they have already presented to the US Food and Drug Administration[12]. "Equally important with finding that our ASOs delay disease in mice is the development of a cerebrospinal fluid prion protein as a biomarker in order to facilitate clinical trials being done in presymptomatic people at risk," says Minikel. "Without this biomarker it would not be clear whether we have a clinical path for ASOs and other PrP-lowering drugs to succeed in trials." The couple aim to forge a new model for primary prevention—intervention before the disease process even begins—in neurodegeneration, and they believe that early constructive engagement with regulators will be key to success in this strategy (Box 2).

Time for collaboration

An important lesson many patient-scientists learn is that when time is of the essence, establishing collaborations is essential. For Gordon, her foundation had to reach around the globe to find just a tiny number of patients with progeria. Projects such as Painter's Count Me In at the Broad are helping with that now as more databases are established. Armed with a database for their disease of interest, new patient-scientists may be able to jump in feet first to tackle their diseases.

It's also necessary to band together to address certain problems. Progress in Duchenne muscular dystrophy, for example, has been hampered by the large variation in how the disease progresses and presents. "I got involved because I went to a public meeting on Duchenne and it was striking how heterogenous the patients' clinical trajectories were," says pharmaceutical business and research advisor Susan Ward. "And as a result, the trials were loaded with noise and variance. We needed a way to get through that."

Today, Ward heads the Collaborative Trajectory Analysis Project (cTAP), which is focused on clinical trial design and analysis. The consortium comprises most of the leading drug developers involved in Duchenne, several advocacy groups and leading researchers. But, critically to the group's mission, Ward recruited statistician James Signorovich of the Analysis Group, a consultancy that specializes in economics, to help the group address the issue of variable disease progression using statistics. "This ties to the larger value proposition of how advocacy groups in rare diseases can drive science," says Katherine Beaverson, senior director, and patient advocacy lead of the Rare Disease Research Unit at Pfizer. "cTAP and its participants share a common goal; by taking this from the analytics side, they are helping all of us—patients, drug developers, academics, everyone."

cTAP is just one sign that the relationship between pharmaceutical companies and advocates is becoming more intertwined. "There was a time where advocacy groups were just trying to get attention for their disease and funding, pharma was really more of a charitable operation for them," says Sharon Hesterlee. Once a patient advocate, she is now executive vice president at Asklepios BioPharmaceutical, a gene therapy company with several programs in neuromuscular disorders. "Today, organizations are starting to contribute to rare disease drug development in new ways; it is much more of a partnership."

Scientist patients are also producing a wealth of information that may prove beneficial for drug programs. For example, the Count Me In group is focused on distinguishing the biology of 'likely responders' to immunotherapies from that of other patients. It has also reviewed the outcomes of six patients who received immunotherapy treatment, two of whom have been disease free since treatment. "And these are all patients with stage 4

angiosarcoma," Painter says. Those are just the kind of data that will help patient-scientists to leapfrog from "rare, untreatable disease" to treatments and even cures.

Research in rare disease may have implications for malignancies as a whole; for example, work at the Chordoma Foundation "contributed to the discovery of a new oncogenesis mechanism [chromothripsis]," Sommer explains, in one of its early papers. That seminal paper helped overturn the idea that oncogenesis was always a stepwise process[13]. "It turns out that sometimes a chromosome can shatter into many pieces and that single event can give rise to cancer," he adds. Those fragments usually cause malignancy[13].

Beyond the science and the resources these patients bring to the table, there is also a certain mindset. "A lot of people who get these types of diagnoses say, 'I don't want to know more'," Giusti says. "But knowledge is a very powerful thing." When she first became a patient, she volunteered for every appropriate research study she heard about. That's how she found out that Takeda's Velcade (bortezomid) was a good option for her before receiving a bone marrow transplant, which is a standard approach to treating this disease at a certain stage.

"It's not just a matter of luck," she says, "It's also matter of knowledge." ❐

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Published online: 1 November 2019
https://doi.org/10.1038/s41587-019-0303-z

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