

When patients march in

Impatient with the slow pace of clinical research, families of individuals suffering from untreatable diseases are taking matters into their own hands—with some success. Virginia Hughes reports.

October 4 was the deadline for biotech giant Genzyme of Cambridge, Massachusetts, to respond to serious claims made to the US government in a petition from three of the company's customers. The petitioners all have Fabry disease and are asking the US Department of Health and Human Services to revoke the company's exclusive license on the patent for Fabrazyme (agalsidase beta), the only drug approved to treat the rare condition. More than a year earlier, a virus in Genzyme's manufacturing plant had tainted production of the \$250,000-a-year drug, forcing the company to ration it. Management first estimated that supply would be back on track within one month. This then became six months. And then—after finding particles of steel and rubber in drug vials—the timelines for full production became even longer.

Genzyme now says it expects to stop rationing Fabrazyme in the first half of next year. As for the petition, after reviewing responses from Genzyme, the government will open up the case for 30 days of public comment, and then issue a decision.

In the meantime, the approximately 1,500 individuals who depend on the replacement enzyme have had to make do with only 50% or less of the recommended dose—not enough to ward off the weight loss, burning limbs and kidney distress that come from the disease. Many are skeptical of Genzyme's announcements and feel betrayed. "Genzyme's promises aren't made so much for the patients, but for the investors—they want projections for this quarter or that quarter," notes C. Allen Black, the Pittsburgh patent lawyer representing the three petitioners. But unrealistic and overoptimistic projections from the company, he says, "have really undermined the trust of these patients."

Ironically, Genzyme's first big success, two decades ago, was thanks to fundraising efforts of families affected by Gaucher disease, another rare disorder. Since then, partly because of evaporating venture capital, patient-generated support of the industry has become more common. At least a half dozen companies have been founded or largely funded by patient advocates, and many large nonprofits are funneling grants directly to private companies. "Patient groups are just coming into all stages of product development, helping to meet the [company's] needs and, in many cases, providing resources to do the necessary studies," notes Stephen Groft, director of the Office of Rare Diseases Research at the National Institutes of Health (NIH) in Bethesda, Maryland.

Patient involvement can change the way a company operates—for better or for worse. Advocates push for faster drug development, expedite recruitment for clinical research, and are compelling lobbyists and advocates in government and regulatory settings. But, as the Genzyme shake-up shows, patient and company interests are not always aligned.

Hollywood endings?

Patient advocates carry with them an urgency and passion that makes the toughest of business problems seem almost trivial. Take John and Aileen Crowley. In early 2000, two years after learning that two of their children had a rare and deadly genetic disease, the couple had raised about a million dollars for various nonprofits supporting research into the condition, Pompe disease. But that investment had not led to any treatments, and the children—Megan, then age 3, and Patrick, 2—were getting worse.

Pompe, a glycogen storage disease that disables muscle tissue, affects fewer than 10,000 people worldwide. Children with Pompe usually can't walk or breathe on their own and, at the time, most did not live to adolescence. "Time was short for us," John Crowley recalls.

Along with the ticking clock, Crowley, then a financial consultant at Bristol-Myers Squibb in Princeton, New Jersey, was concerned that his grassroots fundraising efforts, however successful, would not be enough. "It was going to take many tens of millions of dollars to really move the needle, and I didn't know how to raise that for not for profits," he says. "It was time to back one horse."

The 'horse' was William Canfield, a scientist at the University of Oklahoma Health Sciences Center in Oklahoma City, who had just launched a company, Novazyme, to develop a treatment that would replace the enzyme that is defective in Pompe. Crowley became Novazyme's CEO in March 2000. As recounted in the movie *Extraordinary Measures*, while Crowley sought capital investment—initially \$1.2 million from angel investors, followed by \$27 million in venture capital—Canfield's scientific team steadily plugged away at the bench. The following year, Genzyme bought the company for \$137.5 million—one of the largest-ever biotech deals for a drug that had never been tested in humans.

Canfield's treatment was ultimately not developed, but Genzyme's new Pompe program—led by Crowley—did produce a similar compound, which Megan and Patrick received in January 2003. Within 12 weeks, Crowley says he saw "profound effects" in the children, especially Megan, who could suddenly sit up on her own, type, speak and smile. "For both kids, it saved their lives," says Crowley. He is now working on new drugs for Pompe and other rare diseases as chairman and CEO of Amicus Therapeutics, in Cranbury, New Jersey.

For patient advocates, Crowley's story illustrates the primary upside of getting involved with a private company: it's the fastest route to an actual drug. The arrangement can make sense for companies, too, particularly for small startups.

For example, patients played an invaluable role in the early days of Prosenza Therapeutics, based in Leiden, The Netherlands. In 2002, the company was using a new approach—exon skipping—to find treatments for Duchenne muscular dystrophy, a disease that causes rapid muscle degeneration. Duchenne arises from a glitch in one exon of the dystrophin gene. Prosenza's treatments used an antisense oligonucleotide to skip over additional exons, ultimately producing a truncated, yet functional version of the dystrophin protein.



The 2006 documentary *So Much So Fast* chronicles Stephen Heywood's battle with Lou Gehrig's disease, and the company that his brother, Jamie, launched to find a cure. (Source: West City Films, Newton, Mass.)

The first group to show that exon skipping works was led by Gert-Jan van Ommen, head of the department of human genetics at Leiden University Medical Center. Other scientists in the field were skeptical of the technology, van Ommen says, not least because it was sidestepping the root defect of Duchenne. Fortunately, when his grants were rejected elsewhere, van Ommen received a critical infusion of money from the Duchenne Parent Project, a Dutch advocacy group. His results made a big splash in meetings of the close-knit advocacy community. “If people call me the father of exon skipping, then the Duchenne Parent Project was the mother,” he says.

A few years later, Prosenza—whose vice president of drug discovery had been one of Ommen’s postdoctoral fellows—was pushing the science into commercial development. A half dozen Duchenne advocacy groups, including the Duchenne Parent Project, provided funding, in the form of grants, loans and equity. Company representatives declined to say how much money came from advocates, but noted that even a few hundred thousand dollars can be instrumental in a company’s early stages.

“It allowed us to get funded at a stage of the company that you could not get traditional VC [venture capital] money,” says Luc Dochez, chief business officer at Prosenza. Until recently, he points out, few investors saw opportunities in rare disease treatments because they have such small markets. “But because of the personal investment that these patient groups have, they are willing to take financially riskier bets,” he says.

In this case, the bet paid off. In October 2009, Prosenza licensed a treatment for Duchenne, PRO051, to GlaxoSmithKline, of Brentford, UK, which plans to launch a phase 3 clinical trial later this year.

Patient resources

Even after a company is off the ground, patient support can help industry researchers gain a deep understanding of a disease—its symptoms, course, treatment—and what those who have it need most. Dozens of advocacy groups have launched patient registries and tissue banks, which are important to companies during both preclinical and clinical development of drugs (Table 1). For example, if a certain adverse event happens during the course of a clinical trial, it’s crucial to know whether the symptom also occurs in patients who are not taking the experimental drug. “Creating registries, especially in rare diseases, is an area where patients are really key,” says Hans Schikan, CEO of Prosenza.

One well-connected group is the A-T Children’s Project of Coconut Creek, Florida,

which aims to cure ataxia-telangiectasia (A-T), a degenerative genetic disease that affects muscle control, the immune system and ups the risk of blood cancer. Although the disease affects fewer than 500 children in the United States, the organization has raised >\$26 million. In addition to funding research, it has set up a database of families, several blood, cell and tissue banks, and a clinical center at The Johns Hopkins Hospital in Baltimore, where nearly every new case is diagnosed.

Brad and Vicki Margus founded the effort in 1993, shortly after they learned that two of their young boys had A-T. As the research progressed—the gene for A-T (ataxia-telangiectasia-mutated or *ATM*, a member of the PI-3 kinase family) was discovered in 1995—and the organization grew, Brad Margus, who also ran a successful shrimp company, tired of his dual life. “I’d get one phone call from the president of TGI Fridays, and the next from a Nobel laureate,” he says.

In 2000, he sold his food company and launched Perlegen Sciences, a biotech focused on pharmacogenomics and personalized medicine, which Margus ran until 2006. (The company closed its doors in 2009 after mounting operating losses.) He knew that he wouldn’t be able to get investors interested in A-T, because the market was so small. But his new job at least allowed him to stay near the pulse of biomedical research.

At business dinners with executives from big pharma, he had the chance to pick their brains about A-T treatments. In 2006, he started another company, Envoy Therapeutics of Jupiter, Florida, which focuses on common brain diseases, such as Parkinson’s and Alzheimer’s, but also does some work on A-T. “I’m much closer to what I’m passionate about—how to solve a neurological disease,” Margus says.

There are still no effective drugs for A-T, however. The median age of death is 22, and the Margus boys, long confined to wheelchairs, are 21 and 19. Desperate to develop treatments, the A-T Children’s Project supports a few small private companies as well as basic academic researchers. For instance, it is funding a small Arlington, Massachusetts-based pharmaceutical, MindSet Rx, to do animal toxicity studies of one promising compound. The organization is also backing Edison Pharmaceuticals of Mountain View, California, which has a drug that could be tested in A-T children. Clinicians who work at the Hopkins A-T center are helping Edison file the application to the US Food and Drug Administration (FDA), write the trial protocol and recruit patients, Margus says.

“Even more than money, the thing that’s most critical to CEOs of biotech companies is speed,”

Margus says. He adds that the more organized the advocacy group, the more attractive that particular rare disease will be to industry.

Patents and patients

Patient advocates can speed up regulatory and legal hurdles in drug development, too, by using their considerable power in Washington. In early 2000, Patrick and Sharon Terry were making a splash on Capitol Hill—and in certain legal circles—for being the first patient advocates to be involved in the identification of a gene linked to a disease and the control of the intellectual property surrounding it. Like the Marguses and the Crowleys, the Terrys were abruptly pulled into genetic research after learning that two of their young children had a genetic disease, in their case, pseudoxanthoma elasticum (PXE), a connective tissue disease that can cause heart problems and blindness. When they got the diagnoses, just before Christmas in 1995, little was known about the typical course of the disease, and there were few resources for patients and their families.

So, with the help of an umbrella group called Genetic Alliance, the couple launched a non-profit organization called PXE International. Over the next few years, PXE International distributed research newsletters, coordinated scientific meetings and set up a patient registry and biobank.

Patrick was a construction manager who had overseen a lot of the laboratory projects during the Boston biotech boom. After learning of his children’s diagnoses, he visited the laboratory of Klaus Lindpaintner, a researcher at Brigham and Women’s Hospital working on pinpointing the chromosomal region that is disrupted in PXE. Terry asked if he could help around the laboratory, and Lindpaintner agreed. The first day Terry showed up expecting to wash test tubes. “But I was quite thrilled to find that the postdocs viewed me as another collaborator,” he recalls. For several years, he’d go straight from his construction firm to the laboratory, running gels and analyzing data well into the night. Soon Sharon, too, was working in the laboratory.

In 1997, thanks to samples from a family in the PXE International collection, Lindpaintner’s team pinned *PXE* (now called *ABCC6*) to a locus on chromosome 16 (ref. 1). Three years later, thanks in large part to additional samples from the collection, Lindpaintner and three other laboratories isolated the *PXE* gene (and Sharon, in fact, was listed as a co-author)².

The Terrys convinced all of the groups to turn over their patent rights to Sharon who then assigned her rights to PXE International, so that there would be no restrictions put on

Table 1 Selected blood and tissue banks launched by patient groups worldwide

Organization	Resource
Alpha-1 Foundation < http://www.alphaone.ufl.edu/dna_tissue_bank.php >	Set up DNA and tissue bank (in collaboration with the University of Florida)
Association Francaise contre les Myopathies (AFM), France < http://www.afm-france.org/ >	Set up fourteen worldwide DNA and tissue banks
A-T Children's Project < http://www.communityatcp.org/ >	Established patient registry, and cell and tissue banks; identified mutated gene; created animal models; initiated target discovery and compound screening; established CLIA-certified genetic test; developed clinical end points and standardized scale; orchestrated clinical trials.
Cardio-facio-cutaneous (CFC) International < http://www.cfcsyndrome.org/ >	Developed DNA biobank pivotal in identifying components of the MAP-kinase pathway mutant in this disorder
European Research Network for Alternating Hemiplegia (ERNAH), Austria < http://www.enrah.net/ >	Established an SME project, epidemiological register contributing to orphan drug development, registry of cases of alternating hemiplegia in children in Europe, expert database of research project profiles to promote collaboration
Friedreich's Ataxia Research Alliance (FARA) < http://www.curefa.org/ >	Set up patient registry
Hereditary Disease Foundation (Huntington's) < http://www.hdfoundation.org/home.php >	Established blood and tissue bank; led research consortium; gene discovery; initiated clinical trials
Parent Project Muscular Dystrophy USA < http://www.parentprojectmd.org/site/PageServer?pagename=nws_index > Duchenne Parent Project < http://www.duchenne.nl/ >	Set up a coalition to pool knowledge and resources to accelerate development of treatments for Duchenne muscular dystrophy, established a clearinghouse for research grants and location of research resources, developed global patient registry, global clinical trial network
Pacyonychia Congenital Project < http://www.pacyonychia.org/ >	Established patient registry and research consortium; involved in drug development, orphan drug status and sponsored IND application; recruited patients; collected patient samples
Progeria Research Foundation, USA < http://www.progeriaresearch.org/ >	Created patient registry, cell and tissue bank, and database of patient medical records
Pseudoexanthoma Elasticum (PXE) International < http://www.pxe.org/ >	Created blood and tissue bank and mutation database

Adapted from refs. 3,4.

CLIA, clinical laboratory improvement amendments; SME, small and medium-sized enterprises; IND, investigational new drug.

future licensing of the gene test. This was a smart move, especially in light of what was happening to advocates of Canavan disease, a degenerative brain disorder. In 1993, using patient tissue donations, researchers at Miami Children's Hospital isolated the gene for Canavan's. But in 1997, the hospital acquired an exclusive patent on the gene test, preventing it from gaining widespread use. (The advocates eventually sued the hospital, which settled to provide royalty-free tests to researchers searching for a cure for Canavan's.)

After years in the advocacy world, the Terrys became experienced lobbyists for research on rare diseases. After the human genome was sequenced, Patrick Terry testified in Congressional hearings in favor of gene patents. Sharon is now the president and CEO of the Genetic Alliance, which frequently lobbies on behalf of genetic testing, health privacy and open access to government-funded research.

Through his advocacy work, Patrick Terry became a recognizable face in the fledgling genomics industry. In 2000, he and four other entrepreneurs launched Genomic Health of Redwood City, California, a successful personalized medicine company that makes predictive genetic tests for cancer. Terry now

runs his own consulting company, Technic Solutions in Chevy Chase, Maryland, and advises more than 80 international businesses in the personalized medicine field.

There is still no cure for PXE. PXE International's registry now includes some 3,800 patients and its biobank holds 10,000 samples. The organization has funded considerable research on the mouse model of PXE and on possible treatments for the macular degeneration that affects so many people with the disease. "I'm quite positive that before my children lose their vision, we'll have a treatment," Patrick Terry says.

Conflict management

The relationships between advocates and industry are complicated and often fraught with conflicts of interest—demonstrated most recently by the patient petition against Genzyme over the rights to Fabrazyme. The development and early clinical trials of the drug were done by researchers at the Mount Sinai School of Medicine in New York, and funded by grants from the NIH. Mount Sinai later licensed its patent exclusively to Genzyme to carry into commercial development.

Because the initial work was funded by federal dollars, the petitioners claim that

the NIH should open up the patent to other companies that might be able to produce the drug. Any such company would have to meet regulatory approval and give Genzyme a 5% royalty on Fabrazyme sales.

Even if the NIH grants the request, however, it's not clear whether it would mean that patients get the drug any faster. Another company would have to obtain FDA approval of its manufacturing facilities (though lawyer Black says that, given the circumstances, the agency might expedite the process).

"Producing enzyme replacement therapies requires very specialized biological manufacturing procedures that are not easily replicated, and the process to get a new manufacturing facility approved takes years to complete," notes Jamie Manganello, director of global patient advocacy at Genzyme. Since 2006, Genzyme has been building a second plant, which is slated for regulatory approval in 2011. The facility "places Genzyme in the best position to ensure a sustainable supply of Fabrazyme for the future," Manganello adds.

Manganello declined to comment more specifically on the petition, but notes that the company always strives to be transparent with patients, particularly in the past year. "In this period of crisis, we've worked very

closely with patient organizations to give us feedback,” she says. “In many ways, I view many of the patient group leaders as advisors to Genzyme.”

Despite anybody’s best efforts, it’s immensely difficult to find treatments for diseases—even when patient advocates have executive control. When Jamie Heywood started the ALS Therapy Development Institute (ALS TDI) in 1999, he had only one goal: to keep his younger brother, Stephen, from dying of amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease. He decided that, because there were no strong candidate drugs for ALS, using a typical for-profit structure would not work. “Making money and helping the person you care about are not easy things to do at the same time,” he says.

Instead, he came up with a unique business model, which he dubbed a ‘nonprofit company’: an organization that was run like a company—with a clear vision from the top down—but funded by donors whose goal was not about generating revenue. He only hired scientists from industry because he felt that academic scientists were too wrapped up in developing theories and accumulating publications. ALS TDI would take on risky, noncommercial projects that companies don’t typically invest in, such as validating mouse models and refining high-quality *in vitro* assays.

The Heywoods were fantastic fundraisers, rounding up more than \$10 million in contributions in the first five years. But they spent the money just as quickly. At the beginning, ALS TDI put a lot of effort into gene therapy; later, Stephen received the first stem cell transplant for ALS in the United States (it didn’t improve his symptoms). The Institute’s scientists claimed to screen more potential therapeutics for ALS than all other research laboratories in the world combined.

Although the researchers made a lot of progress in standardizing methods for ALS models, ultimately, none of the experimental treatments panned out. Stephen died in 2006.

Share alike

The year before he died, Stephen, Jamie and their other brother, Ben, began another venture to meet a different unmet need: helping people with day-to-day management of a disease. What was the best way, for instance, to treat anxiety in someone with ALS? How do you deal with excess saliva in a paralyzed patient? “These are questions that the clinical trial architecture wasn’t answering in any way,” says Heywood. “It’s something you can only learn from other patients.”

The brothers launched a website, called PatientsLikeMe (<http://www.patientslikeme.com/>), where patients share their experiences: their symptoms, the effectiveness and side effects of drugs and general quality of life. The information is entered into a web-based interface that classifies disease according to the classical stages used in the clinic. Today, more than 67,000 people have used the site, which offers the service for eight different diseases. All of the information that might be useful to patients is freely accessible. The company sells other services to pharmaceutical and biotech customers, such as design and recruitment of clinical trials, market research for product packaging and analyses of drug safety.

PatientsLikeMe took a for-profit model, Heywood says, because nonprofits don’t have a good track record for collaboration. “In an environment where you don’t have income as your primary objective, and your primary measure of success is moral righteousness, it tends to put people against each other in ways that are less than constructive,” he says.

Marty Tenenbaum, an entrepreneur and melanoma survivor, learned that lesson the hard way. In 2008, nine years after getting his diagnosis, Tenenbaum launched a company called CollabRx. The initial idea was to provide business consulting and systems infrastructure for patient advocates interested in launching ‘virtual biotechs’—organizations that could use the latest medical research to match individuals with rare

diseases to potentially effective, approved drugs or combinations of drugs. The outcome of each of these pairings would be fed back into a central database, so that the data could benefit future patients. Information from one disease could possibly help people with a different disease.

It was a radical new approach, and one that ultimately didn’t work, Tenenbaum says, because foundations—and particularly the researchers on their scientific advisory boards—weren’t interested in signing up. “They saw that any funding diverted to infrastructure and management of projects like this would take away from the money that was available for science,” Tenenbaum says. “So basically everyone said, ‘Great idea, but we’re not ready for it yet.’”

In the past year, Tenenbaum has restructured CollabRx to give personalized medicine advice to cancer patients who have no time to waste. In parallel to this consulting service, later this year the company plans to launch the first phase of Cancer Commons, an online network for sharing case reports, hypotheses and treatment outcomes from research studies.

Despite the hiccups, there seems to be a growing interest in sharing—among patients, industry and government—to accelerate drug development. Genetic Alliance’s Sharon Terry says that one of the primary goals of the alliance is to encourage more companies and researchers to openly share ‘precompetitive’ findings, such as protocols or endpoints of clinical trials, or data about patients who do not respond to drugs.

“We’re interested in increasing the open space, the commons, where we can have precompetitive aggregation of resources, and figuring out how to de-risk that for companies to allow for the acceleration of research,” Terry says.

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