CASE STUDY: A-T CHILDREN’S PROJECT

Designing a Data Platform to Move at the Speed of Advocates
OVERVIEW

In June 2016, the A-T Children’s Project launched the Global A-T Family Data Platform, an effort overseen by A-T families to enable researchers and clinicians to mine large data sets and gain new insights about ataxia-telangiectasia. This rare and progressive neurodegenerative disease affects a variety of systems throughout the body. The data platform collects health, genomic, and other data types about children with the condition.

Though it is still in the early days, the data platform has already demonstrated the impact patient-controlled data can have on accelerating new treatments for patients.

ABOUT A-T

Ataxia-telangiectasia (A-T) is an inherited neurodegenerative disease. A child with A-T begins to suffer from progressive loss of muscle control around the age of 2. Children with the condition become dependent on a wheelchair by age ten because of their inability to control their muscles. Their speech also becomes slurred. Reading and swallowing also become difficult.

Most people with A-T (70 percent) will have some degree of immune system problems. Because of a lack of immunoglobulins—natural infection-fighting agents in the blood—many will suffer from recurrent respiratory infections that can become life-threatening. The weakened immune system and the progressive ataxia can ultimately lead to pneumonia as a common cause of death. About 30 percent of children with A-T develop cancers. Because A-T patients have an extreme sensitivity to radiation, they cannot tolerate standard therapeutic levels of radiation or radiomimetic drugs usually given to cancer patients.

There is no cure for A-T, and there is currently no way to slow the disease's progression. Treatments are directed only toward addressing some symptoms as they appear. Because A-T is a rare disease, little research data is available on pharmaceutical therapies that may aid these children. Physical, occupational, and speech therapy help maintain flexibility, gamma-globulin injections help supplement A-T patients’ immune systems, and high-dose vitamin regimes are used with moderate results.
THE CHALLENGE

The Evolution of the Global A-T Family Data Platform

Brad Margus, founder of the A-T Children’s Project was looking for a data platform that the A-T patient community could use to advance research into the rare condition. Additionally, he was eager to make an ultra-rare disease, like A-T, as attractive to pharmaceutical and biotech companies as possible. He knew that having a robust dataset in place would remove an obstacle that often prevents companies from considering little diseases like A-T. Lastly, it needed to be world-class; removing any excuse companies might use for the A-T community not being ready for clinical development of a therapeutic.

A serial biotech entrepreneur with two sons who have A-T, Margus had grown frustrated by existing registries and wanted to find a data platform that was flexible and dynamic. He believed that patients and their families should be able to answer questions about their experience with a disease initially, but as anecdotal reports pointed to a new symptom or complications, he wanted a system that could query participants as needed.

He also wanted a platform that could handle different types of data, not just data about patients’ health, but lab records, test records, genome sequences, and the new types of data as they arose. If down the road patients were given wearable devices to monitor movement for a month, the platform should incorporate that data as well. With only 400 A-T patients in the United States, it needed to be available in multiple languages to capture as many patients as possible globally.

One of the sources of frustration for Margus, as he surveyed his choices, was the limitations of existing registries on who could access the data. For-profit platforms told him they would provide free access to the data for credentialed researchers, but those researchers would have to apply and demonstrate an acceptable use. When Margus asked about whether drug companies would also have free access, they told him corporate entities would have to pay for access.

Nonprofit alternatives also placed limits on access. For example, one platform that had backing from the National Institutes of Health (NIH) restricted access to only people who were NIH grant recipients.

Margus believed that patients and their families should serve as gatekeepers to their data. He thought they should decide who should have access to the information and didn’t want any single institution, researcher, or physician deciding with whom the data should be shared.

For instance, he said, what if a 14-year-old prodigy in India had an amazing ability to see data patterns? Because of the restriction built into systems, they would not share the data with him because he would not be considered a legitimate investigator.

"What I wanted was a platform that would be overseen by a committee, council, or board of family members who were stakeholders, or parents, or siblings of people with the disease. And then we would have an advisory board that would give us advice when someone requested access to our data to make sure it made sense, but the ultimate decision would still be in the hands of the people who have no conflicts and just want to get the data out there as fast as possible.

-- Brad Margus, A-T Parent; Founder, A-T Children’s Project; Patient Advocacy Advisor, RARE-X"
Another consideration was who would enter the data. A-T Children's Project wanted to allow patient families to enter data rather than relying on a physician or researcher to do so. In the case of A-T, many patients may be outside the United States and may not have access to a rare disease expert. To wait for a patient to see one of the A-T experts would restrict participation, which could serve as an obstacle to obtaining adequate amounts of data needed to generate meaningful findings. Equally daunting for rare disease advocacy groups is navigating the regulatory requirements of patient data. Many disease advocates do not have experience with Institutional Review Boards (IRBs).

At the same time, given that A-T was a small disease population and that people with the condition were spread around the world, having the platform available in multiple languages was essential. While many providers said they could add languages down the road, it was critical and not something that should be put off as something they could eventually do in the case of A-T.

Because A-T is a progressive condition, the organization also felt it was important to give families the ability to update the data with noteworthy changes. Rather than just providing contact information and answering a survey when they joined the data platform, the organization felt it was essential to capture patients’ changes as they occurred.

“When you’re dealing with rare diseases, you need to reach as many patients and have participation from as many patients as possible. Going through a researcher or clinician could be a rate-limiting factor in terms of reaching the numbers that you’d want to see.”

-- Jennifer Thornton, Executive Director, A-T Children’s Project; Principal investigator, A-TCP Data Platform

From time-to-time, the organization also anticipated the need to send out new surveys to ask for information not included in the primary clinical survey provided when someone comes on to the system. It needed to have the ability to push out new questionnaires.

The A-T Children's Project also believed it was necessary to include whole genome sequencing. Though the mutation to a single gene is responsible for driving the condition, there are more than 600 known mutations. People with identical mutations, though, may have different severity of disease. The hope is that by including whole genome sequencing, it may be possible to determine how certain modifier genes may affect the progression of the condition.

Future expansion plans include integrating data from a wristwatch-like digital health monitor that can track people's motion with A-T. The organization is also working on expanding the types of data it captures to include biomarkers in blood that indicate the progression of the disease. Lastly, they are “gamifying” the surveys pushed out to the community to increase participation. For example, when a family answers a question about their A-T child, the platform might tell them what percent of other families who have already answered the way that they have. Families with rare diseases are always eager to know how their experience with the disease compares to others, and being able to receive feedback to their surveys drives greater participation.
Building a Scalable Data Platform Across Diseases

A-T Children’s Project Margus had done some earlier work with the Broad Institute around a genomic data system. He reached out to people he knew there in 2015 to ask if they would help. The institute was a likely place to turn because it had an unusual mix of talent with experience in dealing with the different types of biomedical data Margus needed to capture and staff who were well versed in aspects ranging from the user experience to the regulatory environment.

When Margus talked about his experience working with Broad at a rare disease conference, a long line of representatives of patient advocacy organizations lined up to speak with him as he came down from the stage, all wanting to do the same.

The Broad was soon housing an expanding number of patient groups’ data on its system, but it quickly became apparent the system needed to be made scalable. At first build, it relied on too many people at the Broad having to touch different aspects of a project. Even though each registry was a clone of the other, it took a lot of work to keep each one up and running with threat protection, security, and other things.

“A good analogy is web pages,” said Anthony Philippakis, chief data officer for the Broad Institute and RARE-X board member. “We wanted a WordPress for registries where there’s one platform that’s multi-tenant and it has a lot of registries inside of it, but at the end of the day, you’re just operating one service.”

In 2018, the Broad secured significant funding from an anonymous donor to build out this vision of a scalable version of the system.

The goal is to transform it to where a rare disease foundation could choose their own branding and visual language, build a questionnaire, use a standardized consent form, and create a registry without ever needing an engineer from the Broad to be in the loop.

It is this system that is forming the core of the RARE-X program.
Governance of the Data Platform

Parents participating in the Global A-T Family Data Platform share their child’s medical information and have the option to share a sample of their child’s saliva for whole genome sequencing (WGS). The DNA and health data are analyzed and shared with researchers in a de-identified manner. Participants are apprised of research progress resulting from their participation.

The information on the Global A-T Family Data Platform can only be accessed by qualified investigators. These investigators have been granted permission by a data access committee comprised of A-T family representatives who, in turn, recruit experts for a scientific and medical advisory board, ensuring that each researcher’s project is consistent with the goals of this initiative. The family oversight board oversees the scientific and medical advisory board.

ATCP Data Collection Must Have’s

1. Patients as gatekeepers
2. Patients decide on access
3. Patients can enter data
4. Available in multiple languages
5. Patients can update data at any time – capturing changes as they occur
6. Ability to push questionnaires as needed
7. Access to WGS to help identify subsets of the patient disease
8. Include biorepository data
9. Wearable device data collection
10. Easy and fun user experience
THE RESULTS

A Proof of Principle for Accelerating Research

As an example of the role such a system can play in accelerating research and drug development for rare diseases, consider A-T Children’s Project’s work with a researcher to develop an antisense therapy for A-T. In 1995, scientists identified the underlying gene that is mutated in patients with A-T. That created hope that a gene therapy would be developed eventually. Still, it was later viewed as impractical because the gene responsible for A-T is unusually large and far exceeds the size of vectors used to carry a gene therapy.

When the antisense therapy Spinraza/nusinersen was approved in 2016 for spinal muscular atrophy, A-T Children’s Project’s Margus began considering the possibility of an antisense therapy for A-T. To that end, he reached out to Boston Children’s Hospital’s Dr. Timothy Yu, a physician-scientist who had designed and delivered a custom antisense therapy to a child with a form of the neurodegenerative condition Batten disease.

Dr. Yu thought an antisense approach for A-T was possible. The challenge was that the genetic mutations underlying A-T spanned a spectrum, with some patients having mutations that were amenable to antisense therapies and others who did not.

Understanding Antisense Therapy

Antisense therapies (also known as antisense oligonucleotides or ASOs) are designed to bind precisely with RNA, halting the body’s process of creating a disease-causing protein. ASOs can alter the way our body processes mRNAs, key intermediates in the process by which cells turn DNA instructions into protein building blocks. Depending on how they are tuned, they can block the production of disease-causing proteins, or boost levels of a normal protein. The advantage of ASO medicines is that they are highly specific, and can be developed rapidly and inexpensively, making them a desirable approach to treating rare diseases.
“Using the data that existed in the A-T data platform, Yu and his team were able to produce a catalogue of mutations in about two hours based on about 250 patients in the database whose whole genomes had already been sequenced. They were then able to identify patients with amenable mutations who were still young enough to benefit from an antisense intervention. In the end, they identified a two-year-old girl in California and gave her a first dose of the experimental therapy in January 2020, and she continues to get treatment. The team continues to identify additional patients, including some who have the same mutation as the little girl currently receiving treatment.

It happened really fast,” said Margus. “If we didn’t have this platform, we’d be asking, ‘What do we have to start doing to start piping data?’”

Learnings from A-T’s Experience

Two of the most significant learnings for A-T Children Project’s experience with the data platform relate to implementation and execution issues, rather than the data platform’s design.

The first is that a Field-of-Dreams if-you-build-it-they-will-come attitude won’t work. Patient groups must recruit. To be successful, patient organizations should communicate with their community early on and work to build a coalition of patient families, do so around the world, and get buy-in early to have others help recruit patient families in their countries. If there is a trusted advocate in a country, organizations should educate them about the platform and address any concerns they may have. And, they should understand that this is a never-ending process as there will be newly diagnosed patients that organizations will want to capture. Additionally, the team was sensitive that the platform should not appear to be a solely “American.” They gave it a completely different logo than the A-T Children’s Project, and loaded the family advisory board with almost all non-American parents. As a result, it’s been seen as a truly global program.
“It’s continuous work to remind advocates and families about how important the platform is, and it’s not static,” said A-T Children’s Project’s Thornton. “New kids are being diagnosed, so you need to always be doing outreach to make sure that you’re capturing as many families as you can. It’s a continuous issue.”

The other lesson had to do with the complexities of working with DNA and collecting DNA samples for sequencing. The kit the organization provided had a vial for people to spit into, but this was a problem for younger children unable to spit. People with A-T drool a lot, but it turned out that although parents sent in drool, it did not contain enough DNA material to use. New kits needed to be sent with swabs to capture adequate material to sequence.

Because the organization had an international patient population it needed to capture, it had to learn about the rules and laws governing DNA collection from jurisdiction to jurisdiction and go country by country to work with its commercial IRB to do what was necessary.

One way the organization was able to accelerate the collection of new DNA samples was by attending a patient conference outside the United States and setting up a table. It walked people through the informed consent process with patient families and brought kits to collect samples.

A RARE-X SCALABLE MODEL

RARE-X, working with the Broad Institute and other partners, builds on the pioneering work performed by Broad and A-T Children’s Project to make available a data platform for rare disease patient organizations. RARE-X believes that by enabling rare patient communities to more easily gather, structure, and securely share data through a common platform, it will improve the understanding of rare diseases, shorten the diagnostic odyssey, and accelerate the development of new treatments and cures.

By adapting proven technologies and partnering with leading experts, RARE-X is also bringing forward a federated data analysis platform developed at the Broad, and used in cancer and large population health research initiatives. It is being designed to scale to support the diverse and expanding needs of rare disease research, development, and care in communities worldwide. And, by ensuring clinicians, researchers, drug developers, and patients have access to the right data at the right time, RARE-X will transform the rare disease landscape.

The A-T Children’s Project’s Global A-T Family Data Platform demonstrates a patient-controlled data platform’s power to accelerate the development of needed therapies for rare diseases. By leveraging the technology and making it available to hundreds of rare disease organizations, RARE-X expects to demonstrate the impact of patient-controlled data. Additionally, RARE-X will show how federating data to elucidate connections across rare diseases can provide a deeper understanding of conditions, find relationships previously hidden, and ultimately provide patients with the treatments and cures they seek.
Special thanks to the following people and organizations for their input and collaboration -

• Daniel Levine
• A-T Children’s Project
• Brad Margus
• Jennifer Thornton
• Anthony Philippakis, M.D., Ph.D.
• The Broad Institute
• Timothy Yu, M.D., Ph.D.
• Ethan Perlstein, Ph.D.