NEWBURY, Mass. – Andy Tranfaglia seemed to be getting better by the day.

He stopped vomiting his meals. His coordination improved enough that he could return a volley on the tennis court. His agitation receded. Instead of seeing every new person as a threat, he began to see them as a possible friend.

His parents, of course, were thrilled. For more than two decades, they had turned their professional lives into a search for treatments for their son's condition. They raised money, cajoled researchers and supported clinical trials such as the one that finally was making a difference for Andy.

Until it wasn't.

Six weeks after he started showing improvements, most of them went away.

The first sign was the return of his reflux.

"That was a terrible blow," said Andy's mother, Katie Clapp. "To see the window and then see it go away was depressing."

Despite that research failure in 2014 and others before and after, the fact that Andy improved at all gave the family optimism. Maybe they weren't just chasing dreams. Maybe they really could make life easier for Andy and others like him.
That renewed hope still keeps them going.

‘We do what’s needed’

Andy was born in June 1989 with a condition called Fragile X Syndrome, caused by a gene mutation that prevents production of a vital protein called FMRP crucial for sending signals between brain cells.

Clapp has a "premutation," which means she isn't impaired but can pass on the condition.

The gene she inherited from her mother, who inherited it from hers, might be beneficial in some ways. People with it are often driven and successful, according to Dr. Randi Hagerman, a leading Fragile X researcher at the University of California, Davis. "They do marvelous things."

CHOOSING HOPE

The second in an occasional series exploring how scientific advances are transforming care for rare diseases.

But like many others who get the full Fragile X mutation, Andy suffers from a long list of medical conditions, including seizures, severe anxiety, reflux, autism, vertigo, obsessive-compulsive disorder and intellectual disability.

He has a measured IQ of 42 on a scale where the average hovers under 100.

Andy's diagnosis, shortly before his third birthday, devastated Clapp and her husband, Dr. Michael Tranfaglia, who had met their senior year at Harvard.

A few weeks after the diagnosis, Clapp and Tranfaglia attended their first Fragile X scientific conference and got hooked. They met Hagerman, the men who had discovered the Fragile X mutation and other prominent scientists all trying to understand the condition that afflicted their son and maybe as many as 1 million others worldwide.

Clapp and Tranfaglia discovered that Fragile X was potentially treatable, but too few researchers were working on treatments. At that pace, a solution would take forever. They decided to help speed things along.

In 1994, with their younger, healthy daughter, Laura, in tow, they set up a foundation to pursue medical treatments themselves. Drugs could treat symptoms such as anxiety and reflux, but nothing touched the root
problems. Maybe more investment in basic research could lead to a deeper understanding of the condition and how to treat it.

Clapp thought it would be a five-year volunteer effort and they'd have Fragile X figured out.

Twenty-seven years later, they're still chipping away at the condition that dominates every aspect of their lives.

Over that time, with the help mostly of Fragile X parents, their organization, FRAXA, has raised $31 million and provided 614 research grants to scientists in 19 countries. Other research organizations contributed funds and effort, including the Simons Foundation for Autism Research Initiative, the Azrieli Foundation and the National Fragile X Foundation.

FRAXA has three full-time employees, including Clapp and Tranfaglia, and two part-time employees.

"I'm the brains behind the operation," Tranfaglia joked while sitting on a leather couch in their suburban living room. "And I'm his boss," Clapp answered without missing a beat.

A psychiatrist, he's the medical director and chief scientific officer, "chief cook and bottle washer and air-conditioning repairman."

"We do what's needed," Clapp added.

‘An exciting time’

Only about one in 10 experimental drugs proves its worth and makes it through the federal approval process to patients.

"Which means we have to fund at least 10 trials before we get all discouraged," Clapp said. "You just can't stop at the first one."

They've funded an even dozen clinical trials. No. 11 may turn out to be the one that makes it all worthwhile.

In that study, started in 2018 and published this spring, 30 adults with Fragile X showed average IQ gains of 10 points in 12 weeks on a drug made by a company called Tetra Therapeutics.

"That's huge," Clapp said. If Andy gained 10 IQ points, his whole quality of life would change. "It’s just amazing to think of."
She wants to enroll him in a larger, more definitive trial of the drug set to start this summer. It will be Andy's first since his unsuccessful experience seven years ago. His uncontrolled seizures disqualify him for most research trials.

Progress is coming – on Fragile X and other brain conditions – that could change the trajectory of many families' lives.

"It's an exciting time in pediatric neurology," said Dr. Elizabeth Berry-Kravis, a professor at Rush University Medical Center in Chicago who led the Tetra trial among others in her more than 30 years of working on Fragile X.

Scientists understand these conditions better at the molecular and genetic level and what biological processes to target. Advances in drug development and how to design an effective study mean trials are more likely to succeed. Families are eager to volunteer for trials that move the field forward.

Still, developing a treatment has outlasted childhoods and professional careers, and there's no approved drug to justify all that effort.

Why stick with it through failure after failure, year after year of redoubling patience and recalibrating dreams?

“You can’t give up on your kids,” Clapp said.

‘Go see Barbara now’

Every morning, Andy wakes up in his sparsely decorated second-floor bedroom. If there are too many distractions, it will prevent him from sleeping. There’s just a dresser, a wallpaper border left over from early childhood and a bookcase, empty except for three pairs of shoes.

He dresses himself, then scoots on his bottom down the carpeted steps. The stairs, which cut through a brightly lit two-story atrium, must look like a cliff's edge to his son's eyes, Tranfaglia said, because of his vertigo.

Sometimes Andy, 32, fixes himself breakfast. On a recent morning, when his mother found him in the kitchen around 7:30, he declared he was hungry and waited for her to warm him sausages and leftover butternut squash.

He needs help shaving and must be persuaded to brush his teeth, take a bath or shower.
Andy also has his strengths. He loves being around animals and spends part of every day helping to care for donkeys and horses. Collecting the recycling and putting it in the proper bin at the town's collection center gives him great satisfaction. "It makes sense to him," Clapp said.

By 8:15 a.m. or so, Andy is ready to leave for the day, though he isn't expected at his caregiver Barbara's for 45 minutes and it's only an eight-minute drive. He repeats "Go Barbara's" often over the next half-hour.

"No key," he quietly announces when they finally get in the car. It takes a few seconds before his mom realizes she needs to go back inside for the car key.

He looks out for pedestrians as Clapp backs their Toyota RAV4 out onto their street and then for cars as she pulls onto a busy road. "Car," he repeats until it's clear.

They stop at the recycling center, then to look at a small herd of buffalo housed on a nearby farm.

"I see babies. See 'em?" Andy says. "See 'em?"

He tends to obsess, or in technical terms "perseverate." He repeats questions again and again. He speaks quietly and often pulls both arms up to his face and hunches over, as if to hide in embarrassment.

"I go see Barbara," he says. "I wanna go see Barbara now."

Once in Barbara's barn, she pours food into a bucket, and Andy slips it through the wooden bars of each stall. She keeps up a running commentary of her activities, and he repeats a few of her words.

"Shall we feed them some carrots?"

"Carrots." He finds the carrots and holds one out to the donkey, Desi, who grabs it hungrily with his lips.

He helps her distribute small bales of hay to each of the animals.

"What's next?" Barbara asks him. "What comes after the hay?"

Andy doesn't answer but correctly reaches for the hose to fill their water dishes.

‘Like running a marathon'
For even longer than Andy's parents have struggled to find treatments, a handful of scientists have been looking.

Berry-Kravis said she decided when she was a seventh grader that she wanted to understand the chemistry of the brain. At 63, she's still at it.

Fragile X researcher Elizabeth Berry-Kravis was fascinated from an early age by the workings of the brain. "Drug development in Fragile X is like running a marathon," said Berry-Kravis, who has run two herself.

Hagerman, a distinguished professor of pediatrics at UC-Davis and medical director of the Medical Interventions for Neurodevelopmental Disorders (MIND) Institute there, said she feels growing pressure to succeed.

"I want to push these new therapies soon so that I can make a difference in the lives of my patients before I retire," she said. "I'm getting old."
Fragile X researcher Randi Hagerman is determined to "make a difference in the lives of my patients before I retire."

Mark Bear, a neuroscientist at the Massachusetts Institute of Technology, was a strictly lab-bench, basic science researcher in 1999 when he stumbled across a brain signaling mechanism he thought might be key to Fragile X.

His lab was studying how signals cross the gaps between brain cells, called synapses. In Fragile X, the signals can't cross synapses as easily as they should because of a flaw in the chemical pathway. Restore that pathway with a drug, and it should normalize the messaging, Bear thought.

The theory worked incredibly well in scores of studies in mice, rats and fruit flies, and it looked good in preliminary studies in people. It excited folks at a company Bear co-founded called Seaside Therapeutics and at major drug companies such as Roche and Novartis.
"We were convinced it would work," said Florian von Raison, a Novartis executive who ran two simultaneous trials based on Bear's work from 2010 to 2014. The trials included about 300 teenagers and adults with Fragile X from all over the world, including Andy.

Translating basic science into people is harder than it looks, Bear said. There was so much he and others didn't know – couldn't have known – more than a decade ago when the human trials began. Mouse studies couldn't show what dose might be effective in people, what age made the most sense to treat, how long the treatment should last and what else might be combined with the drug to make it more effective.

Still, just as Andy benefited temporarily from the Novartis trial, some people with Fragile X improved on Roche's and Seaside’s drug.
"That drug was life-changing for us," said Holly Usrey-Roos of Canton, Illinois, whose son, Parker Roos, 22, started stringing words together for the first time during the Seaside trial. "I waited 10 years to hear him talk in sentences."

Roos kept that ability after the trial ended, though he talks mostly about his favorite team, the Chicago Cubs.

When results for all three companies' trials were unveiled, there was no statistical difference between improvements seen in those who received the active drug versus those given a placebo. "It was really hard to see those data," said von Raison, head of clinical development in neuroscience for Novartis' global drug development team.

The brain is clever. When one pathway is blocked, brain cells adapt and take another route to the same result, Bear said. "Nature works hard to thwart us from intervening."

Roche and Novartis closed their Fragile X research programs in 2014. Seaside folded.

"While it was devastating to lose (the Seaside drug), it renewed our faith in the researchers who have dedicated their lives to helping our loved ones," said Usrey-Roos, who started working for FRAXA in April. "Through the devastation of what we were losing, we had more hope than ever that this was just the start of what was to come."

Progress has fed that enthusiasm.

Behavioral, language and physical therapies for people with Fragile X have improved in recent years, Hagerman said.

"We think we're moving on all fronts, not just medication," she said.

Hagerman is running trials in three centers to see whether the diabetes drug metformin can help people with Fragile X, including improving IQ. "In anecdotal instances, it's really quite positive," she said.

Gene therapy is potentially transformative. By editing brain cells, the treatment could replace the faulty gene with a normal one and provide the missing FMRP protein.

"That's probably the best way to achieve the objective," said Bear, who started a company and is getting ready for a trial. Gene therapy might cure
babies of Fragile X and offer dramatic improvement to adults such as Andy. "That would be fantastic."

Gene therapy was Clapp and Tranfaglia’s initial plan for a cure nearly 30 years ago.

"It'll come. But we're not going to sit around and wait for it," Clapp said. "That would be maybe 10 to 20 years down the road. Who knows?"

‘The first unequivocal success’

In 2015, Mark Gurney was running a small biotech with a drug aimed at treating Alzheimer’s when he came across a Fragile X scientific paper, co-written by Tranfaglia.

Gurney wondered if the same brain circuit his Alzheimer’s drug addressed might help target the malfunctions in Fragile X.

The only way to find out was to test the drug in animals. Gurney’s eight-person company, Tetra Pharmaceuticals, didn’t have access to mice with the Fragile X mutation. So FRAXA, working with a lab in Chile, ran them.

"It was a critically important contribution," Gurney said. "We may not have considered Fragile X otherwise."

Results looked extremely promising. Mice with the same genetic mutation as people with Fragile X who got the drug were no longer hyperactive. They became more sociable and started making nests. The longer the mice got the drug, the more they improved.

In 2018, FRAXA helped Berry-Kravis launch a trial of the drug.

Berry-Kravis had given birth to her second child, a boy, in October 1990. Two days later, she hurried back to her lab to finish up a breakthrough project. After two years of tedious research, she had figured out that a signaling molecule related to learning and memory was abnormal in Fragile X cells.

Tetra’s drug targets the same pathway.

Last fall, the week her radiologist-in-training son turned 30, she saw the first results from Tetra, now owned by a Japanese pharmaceutical company.
Failure remains a possibility, but this win suggests a treatment for the underlying symptoms of Fragile X may finally be near.

"This is the first unequivocal success," said Tranfaglia, who is eager to see Andy join the larger trial. "We're an overnight sensation after 27 years ... we finally got lucky."

Even without a miracle therapy, Andy is doing much better, Clapp said after dropping him off at Barbara's farm that recent morning.

Andy's worst period was just before starting puberty and for about a decade after. He would have meltdowns when he was overwhelmed or afraid. He'd simply drop to the ground, refusing to get up, though he might be in a horse's stall, a busy driveway or – once – the Logan Airport no-parking drop-off zone.

Clapp is still on edge when she takes Andy out in unfamiliar places or to meet new people, but his last major meltdown was more than two years ago. "He's come a long way," she said, probably because of maturity, his terrific caregivers and the right combination of medications to treat his symptoms.

She's probably adjusted, too. "Maybe some of this is a touch of acceptance," Clapp said. "This FRAXA stuff is finally paying off, though we're still looking for our perfect drug – or our imperfect drug."

Contact Karen Weintraub at kweintraub@usatoday.com.

Health and patient safety coverage at USA TODAY is made possible in part by a grant from the Masimo Foundation for Ethics, Innovation and Competition in Healthcare. The Masimo Foundation does not provide editorial input

This article originally appeared on USA TODAY: Fragile X treatment: Decades later, progress in rare genetic condition