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SPECIAL REPORT

A decade ago, these drugs tore apart the FDA. Today, they might be some patients' best hope

Once-divisive 'exon-skipping' treatments for Duchenne muscular dystrophy are showing startling promise

By Jason Mast

Mast, who has reported extensively on rare diseases for four years, spoke with Debra and Hawken Miller more than six times over the last eight months and interviewed more than a dozen other advocates, researchers, executives, and former FDA officials for this story.

A year after the worst day of her life, Debra Miller received a voicemail she couldn't quite make out. In a thick accent, a man said something about research and left a phone number. She called but couldn't get through. "I didn't know what country code to put in," she said.

Debra moved on, but the voice kept tumbling through her brain. She was desperate. Her first child, Hawken, had been diagnosed 13 months before with Duchenne muscular dystrophy. In blunt tones she would never forget, a doctor had told her that her 5-year-old boy would slowly lose the ability to walk and die by 18.

When she finally figured out the digits, a Dutch scientist explained he was launching a startup around one of the most counterintuitive ideas in modern genetics: that sometimes you can fix a broken gene by breaking it just a little bit more.

That strategy, known as exon skipping, would taunt Debra for two decades, always promising a therapy just out of reach. It prompted her to raise $1.3 million for the Dutch scientist and helped turn her fledgling advocacy group, CureDuchenne, into a powerhouse. Eventually, the idea spread far beyond the Netherlands and Debra's home in Newport Beach, Calif., stirring tenuous hope for a life-altering treatment.

Exon-skipping drugs sparked a civil war within the Food and Drug Administration. Under pressure from advocates and companies, a top official overrode reviewers to approve the first of several candidates. One company, Sarepta Therapeutics, has since earned over $5.5 billion from drugs that may or may not provide much benefit.

Throughout, by the fickle winds of scientific misfortune, mother and son remained waiting — until about two and a half years ago. That's when Hawken enrolled in a clinical trial for a new exon-skipping drug Debra helped support. The results from him and 38 other patients have since stunned some of the field's top experts.

SANDY HUFFAKER FOR STAT

Hawken Miller at his home in Newport Beach, Calif.

The data "is fairly astonishing," said Stanley Nelson, co-

director of the Center for Duchenne Muscular Dystrophy at UCLA, who was not involved in the study. “I would not have predicted that.”

Novartis agreed to buy Avidity Biosciences, the company behind the drug, for $12 billion in October and plans to file for approval this year. The medicine, known as del-zota, can only treat about 900 of the 15,000 Duchenne patients in the U.S. But it is the first of a wave of new drugs that could eventually alter the lives of over 60% of all Duchenne patients and tens of thousands facing other neuromuscular conditions.

Startups have reinvented a class of medicines Debra first supported as a young mom. The earlier molecules, while elegant on paper, passed through patients like a cup of coffee, barely penetrating their muscle cells.

So scientists went back to the lab. Some outfitted the molecules with antibodies that, like biological homing missiles, guide them to muscle. Others rearranged the atoms until they found a combination that slid more easily into tissues. The results are compounds that, per company data, are vastly superior at restoring dystrophin, the missing protein in Duchenne.

These drugs will not change muscular dystrophy overnight. Companies will need to navigate an FDA upended by The Trump administration. They will need to run large, randomized studies to convince skeptical experts, who have seen other Duchenne drugs — most recently gene therapy — fail to deliver the transformative results teased by early data. (Randomized trials for four of the first wave of exon-skipping drugs have also failed, including one that induced significant dystrophin levels.)

“I’m a little more jaded,” said Sharon Hesterlee, president and CEO of the Muscular Dystrophy Association and a longtime Duchenne researcher, calling the results from the new exon-skippers an improvement and “very encouraging.”

And they will need further improvements. Some mutations are more “skippable” and thus more treatable than others. For the mutations targeted by other drugs reaching regulators this year, from Dyne Therapeutics and Wave Life Sciences, the best they will do is slow an inevitable decline. “These are still low levels,” said Nelson.

Debra knows the limitations. Avidity’s drug, though, has already changed her son’s life. Hawken grew up determined to think less about Duchenne than about football, wildlife photography, and missionary work. He made peace with a disease that slowly robbed him of his ability to run and walk and, finally, of his dream career. Tomorrow, as his faith reminded him, is promised to no one.

Now 29, he will always use a wheelchair. He may always rely on caregivers. But the drug has let him imagine, again, what he might do with the tomorrows that may come.

The lucky error of exon skipping

Steve Wilton remembers Debra Miller vaguely. After conferences in the 2000s, he’d hang out at the nearest bar, as a parade of moms approached him holding a card with a photo of their boy on one side and his mutation on the other. Can your strategy help us, they asked.

Wilton, a crass, fast-talking researcher who worked out of a leaky, converted tuberculosis ward in Western Australia, looked at each and rendered a verdict: yes, no, maybe. He tried his best to explain why, sketching abstracted molecular genetics on napkins.

They were tough conversations. In the early years after dystrophin’s isolation in 1987, scientists and parents focused on conceptually straightforward but ultimately disappointing fixes: gene therapy, muscle cell injections from donors. Exon skipping was more nuanced, a subtle manipulation of the genetic alphabet.

Dystrophin is an 11,000-letter gene, spread across 79 fragments called exons. It’s supposed to spell out instructions for building a shock-absorber protein, also called dystrophin, that cushions muscle cells against the force of their own contractions. The cell reads three letters at a time. Most sequences refer to a different amino acid that cellular factories have to string together; a few combinations act as stop signs.

Most Duchenne patients aren’t missing the instructions for some essential part of the protein. Instead, some small error has rendered these instructions illegible. Consider, for example, what happens if just a single letter goes missing. Every subsequent three-letter combo would change. An eons-old blueprint for constructing a protein essential to human life becomes monkey-keyboard nonsense.

In the early 1990s, though, researchers discovered that some boys produce trace amounts of protein, thanks to a second, fortuitous error: As their cells transcribed the gene, they

Newer drugs restore more dystrophin

Old vs new generation of exon-skipping drugs

Drug	Company	Modality	Exon	Dystrophin Total	Status
Approved					
Viltepso	NS Pharma	First Generation	53	5.9%	Approved
Amondys 45	Sarepta	First Generation	45	1.7%	Approved
Vyondys 53	Sarepta	First Generation	53	1%	Approved
Exondys 51	Sarepta	First Generation	51	0.4%	Approved
Experimental					
Del-Zota	Avidity Biosciences/Novartis	TFR Antibody-Targeting	44	32%	Filing this year
Brogidirsen	NS Pharma	Next-gen chemistry	44	24.5%	In clinical trials
WVE-N531	Wave Life Sciences	Novel Chemistry	53	7.8%	Filing this year
SRP-5051	Sarepta	Cell-penetrating peptide	51	5.2%	Discontinued
Z-rostudirsen	Dyne Therapeutics	TFR Antibody-Targeting	51	5.5%	Filing this year
BMN 351	BioMarin	Next-gen chemistry	51	5%	In clinical trials
PGN-EDO51	Pepgen	Cell-penetrating peptide	51	0.6%	Discontinued

Dystrophin levels shown as a percentage of normal, healthy levels. Different companies use different methods to measure dystrophin, test different doses, and target different mutations. Results not directly comparable.

Table: J. Emory Parker/STAT

skipped over another fragment before or after the mutation. It was a math trick. Rather than scramble the gene further, the mistake restored the proper three-letter sequence, leading to a smaller but apparently functional protein.

In 1998, Wilton flew to an advocacy meeting in Pittsburgh to announce he could induce exon skipping, with drugs, in the lab.

"It appeared to us as a sort of 'Star Wars' kind of thing," said Pat Furlong, head of Parent Project Muscular Dystrophy (PPMD), the advocacy group, who recounted the meeting. "We were surprised by the genetic capability."

Afterward, every parent wanted to know if their child had the right kind of mutation. Hawken, Wilton told Debra, had the best mutation. He lacked exon 45, which could be treated by skipping exon 44. For whatever reason, muscle cells skipped over exon 44 the most, an effect drugs would only amplify.

'What have I done?'

For Debra, Wilton's message was a rare bit of clarity in the blur that had become her life. For two years, she heeded the doctors who said her only child was fine. She interpreted his sluggish pace on the soccer field as youthful laziness.

"So I took him to the park and made him run wind sprints and pushed him as hard as I could," she said. "Then when we got the diagnosis, it was just a gut punch to me. Like, 'Oh, my God, what have I done to this poor little guy?'"

In 2002, when Hawken was 5, a family friend suggested a $15 blood test. It measured levels of the muscle enzyme creatine kinase, a sign, like rubble in the river, of how quickly muscle cells were collapsing. Healthy adults generally have between 22 and 200 CK units per liter. Hawken's result: 30,000.

Debra was a wreck for weeks. Her husband, Paul, spent many of his days in Arizona, where he worked as a food industry executive. Debra tried to put on a smile for Hawken and put him through daily physical therapy, while ducking into the closet to cry and pray. It was there, on her knees one day between two racks of clothes, she said she felt a presence come to her. Get up, it said. Move forward.

Debra, who is Christian, read scientific publications on two hulking monitors, perched in Hawken's playroom, she otherwise used to trade stocks. In college, friends accused her of monomania. Now she had a new target. She attended every academic and advocacy meeting. In October 2003, she and Paul decided PPMD and other groups weren't moving fast enough or with enough business savvy and founded CureDuchenne.

"If things didn't turn out well for Hawken, I wanted to know that I did absolutely everything possible that I could do for my son," she said.

Two months later, the voicemail came. It was the CEO of a fledgling exon-skipping startup out of Leiden University, called Prosensa. He wanted to start with Hawken's mutation. The Millers raised the money over 18 months and flew to the Netherlands, where researchers plucked Hawken's skin to create cells they could study potential drugs against. He still carries the scar and a vague memory of scurrying lab mice.

Then the CEO called back. Prosensa was pivoting. Hawken's mutation was too rare. Financially, Prosensa needed to prioritize exon 51, which might treat 13% of all Duchenne patients. Hawken, the CEO assured her, would be right behind. "The news came with a lot of promises," she recalled.

'Wildly unrealistic expectations'

Books could be written about the decade that followed: the tantalizing signs of efficacy, the frenzy in labs and boardrooms, the hammering of the FDA, the debate it all kicked up about how stringent regulators should be in the face of a fatal disease and desperate families.

In short, the drugs likely worked — barely. They produced minute amounts of dystrophin. But Prosensa and Sarepta, a long-struggling biotech that teamed with Wilton, and their academic partners made very different claims: that patients on their drugs made anywhere from 15% to half of the protein levels found in healthy individuals.

These claims, combined with reports of children falling less or walking longer after entering trials, sparked an advocacy campaign of a force and agency-sieging tenor not seen since the AIDS crisis. Moms told reporters about their dying children and the treatment that might save them. They collected their own data, accosted FDA reviewers at conferences, and testified before Congress.

Years later, researchers from the two camps still point fingers. "The Dutch and Prosensa were absolute masters at manipulating facts," Wilton said.

Throughout the fervor, Debra and Hawken remained waiting. Deadlines from Prosensa were missed, reset, and missed again. In later years, Debra would see these days as a crash course in the plodding, circuitous path of drug development and the sacrifices she would have to make trying to fight both for her son and 15,000 other boys.

But in that moment, she said, "I got less than nice about it."

In 2010, the company opened an exon 44 trial in Europe. Twice, the family flew to the continent — first Belgium, then Italy — to enroll Hawken. Twice, their invitations were abruptly pulled, after, Debra was told, other advocates intervened and argued they would be taking another boy's spot. (The ethics here are complicated, several scholars said. But broadly speaking, patients in families who helped fund trials should still be eligible for them, even if it's in another country, so long as they fit other criteria and are not bumped to the front of the line.)

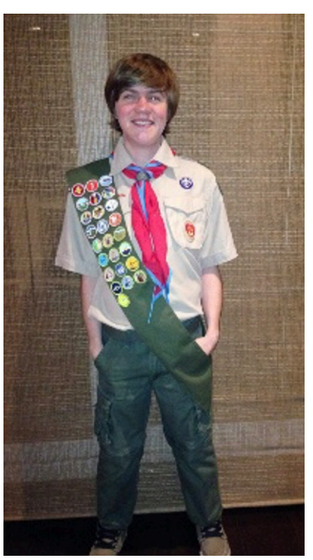
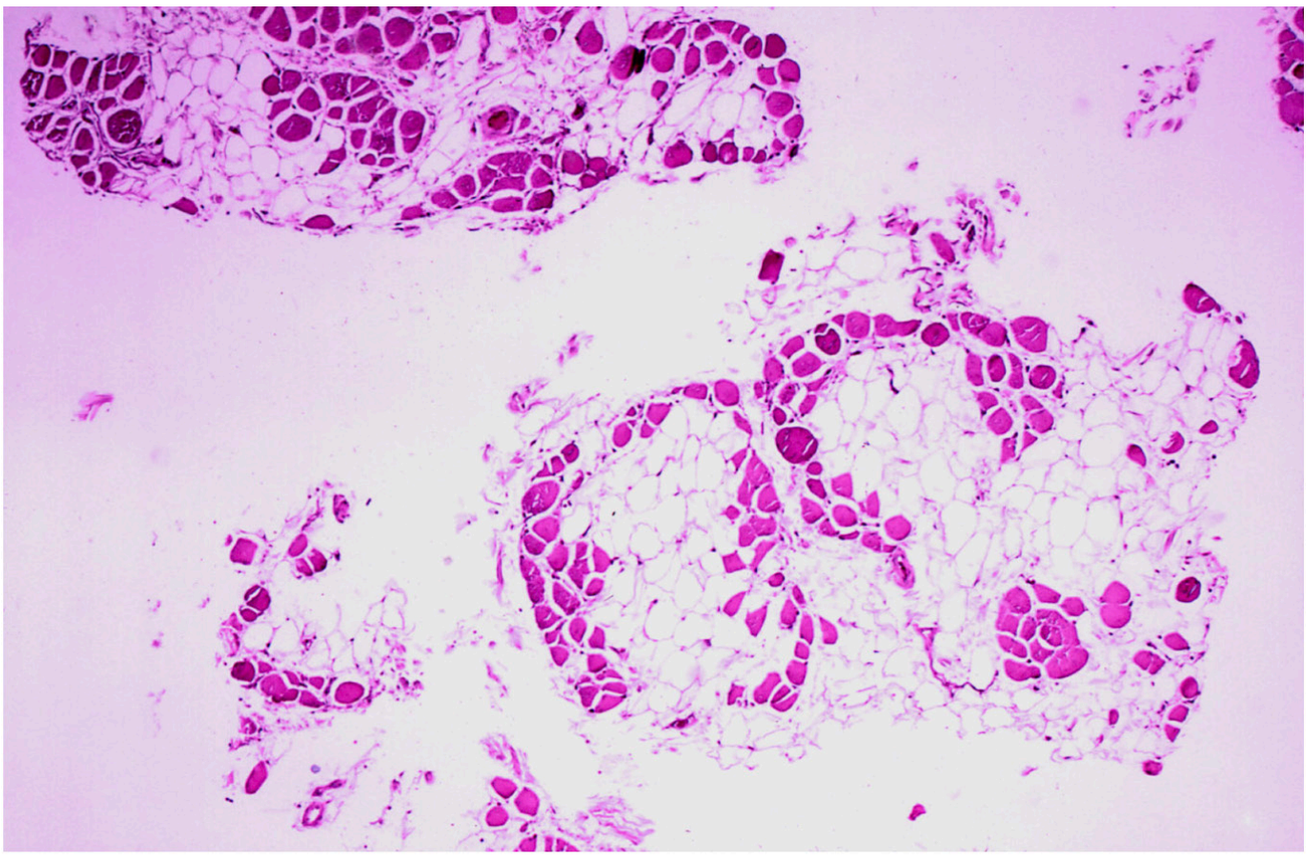


PHOTO COURTESY MILLER FAMILY

Hawken Miller at age 18, just after qualifying as Eagle Scout.

Hawken, meanwhile, had grown up. He was a teenager. His muscles' own natural exon skipping and his strict, mom-imposed, broccoli-and-lean-meat diet slowed his



A cross section of a leg muscle from a person with Duchenne muscular dystrophy. The photo, taken in 1972, has long been used to illustrate how muscle fibers break down and are replaced by fat in the disease. Dr. Edwin P. Ewing, Jr./CDC

descent. In elementary school, he could cut it as a goalie at soccer.But with age, he'd start to feel his legs turn to concrete on long walks.

He did what he could. He swam and played ping-pong. He camped with his father and the Boy Scouts across California, sometimes riding on Paul's back, and earned his Eagle medal with whatever badges he could complete. After his parents bought him a Game Boy Advance for the trip to Leiden — a distraction, in a pre-iPad era, to keep him occupied at dinners — he found video games, virtual worlds where he was not so limited.

And he found meaning. The Millers were churchgoing people, and there, in the pews, he heard how Jesus ministered to the adulterers, the tax collectors, the people cast out by society, who had nothing. It resonated. When his eighth grade teacher asked the class to write versions of NPR's "This I Believe" series, he described his struggles and his faith. He volunteered to read his in front of his class, but a friend had to finish it as Hawken wept.

"I realized, I think earlier than a lot of people, that life is so fragile, we really aren't in control of anything, and everything we do is a gift from God," he reflected recently.

In 2015 and 2016, the FDA held hearings to review drugs from both Sarepta and Prosensa, which by then had been bought by BioMarin for $680 million despite a failed Phase 3 trial. In painstaking detail, FDA statisticians walked through flaws in both companies' data, showing their drugs produced almost no dystrophin. Debra, who had also given a grant to Sarepta, testified at both, arguing — by pointing to Hawken's natural skipping and slow decline — that even those trace amounts of dystrophin could slow the disease.

Most of the community coalesced around Sarepta, though. Prosensa's drugs left painful, scarring welts on the skin. Sarepta's drug seemed safe. In 2016, the agency rejected Prosensa's drug. Eight months later, Janet Woodcock, the agency's top drug official, approved Sarepta's treatment, Exondys 51.

In a dissenting review, Ellis Unger, a top staffer, said a since-discredited study from 2013 "raised wildly unrealistic expectations in the DMD community." He called Exondys a "scientifically elegant placebo."

The company would go on to charge some patients well over $1 million for Exondys and get two similar drugs approved for other mutations, even as it missed deadlines to complete FDA-mandated trials to prove these medicines helped patients.

Debra left the fight bitter. She was fed up with advocates who hadn't helped her push for Prosensa's drug. Just before BioMarin bought it, Prosensa opened an expanded access arm for exon 44, finally allowing Hawken to get treatment. Now, it was abandoning those programs and Sarepta, still barely solvent, had nothing near trials for Hawken.

She looked into whether CureDuchenne could make

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Hawken and Debra Miller, photographed in February, say they've changed their ideas of what comes next.

BioMarin's exon 44 drug itself, but it was too complicated. Hawken stopped his infusions. Neither were sure if it had done anything.

Discovering a key for exon-skippers

It wasn't a mystery why exon skipping disappointed. The drugs barely penetrated patients' muscles. Researchers had been misled by mice and by their own slipshod methods for measuring dystrophin.

In reality, much of what Sarepta injected into a patient is quickly flushed into the kidneys or bladder. "They're a very good way to make really expensive urine," said Annemieke Aartsma-Rus, an exon-skipping researcher at Leiden University.

Scientists had tinkered for years with ways of guiding these medicines into muscle. Exon-skipping molecules themselves are just short DNA-like strands. Inside a cell, they can smother genes as they're being transcribed. Outside the cell, they are flotsam caught in the bloodstream's flow. But what if you tethered them to a peptide, like one from HIV, evolved for seamless cellular infiltration? The results from Wilton and others were riveting. But the drugs eventually damaged kidneys.

In San Diego, at a small research lab overlooking Torrey Pines Golf Course, Art Levin had another idea. An itinerant, avuncular chemist, Levin served as a scientific consigliere for Miller and other advocates. On occasion, he'd talk at length on the phone with her and her team, vetting various investment ideas. He assisted at Prosensa's FDA hearing.

His latest startup, Avidity NanoMedicines, was trying to encase similar DNA-like molecules in nanoparticles. Theoretically, the particles would be equipped with antibodies that guide them to tumors, to silence mutant, cancer-causing genes. But they fell apart in chemists' hands. "The antibodies kept floating away," said Levin, who was chief scientist.

One day, as their resources dwindled, an Avidity scientist decided to just glue the antibodies directly to the DNA-like molecules. To Levin's shock, it worked. The amount of drug that reached the tumor increased seventyfold.

It's not enough, though, to get to the cellular door. The drug has to enter and interact with the genetic machinery. For drug developers, this step remains a hazy, occult process. But one way of getting there is picking the right door, the right receptor on the cell surface. "It's a little bit of a black box," said Levin.

A group from Japan's Takeda Pharmaceuticals published data showing that targeting transferrin, an ancient protein responsible for pulling iron into our cells, could serve as that gateway in muscle. Levin read the paper and saw the potential: a way not of curing tumors, but of making exon-skippers finally work.

Still, he hesitated to say anything publicly, including to Debra. The last battle had left its mark. "So many people have so much hope riding on those compounds," he said.

Avidity barely survived long enough to work out its mechanism — at one point Levin was buying pipette tips on his personal credit card — but by 2019 the data looked solid. Avidity, now rebranded as Avidity Biosciences, secured a deal with Eli Lilly. Then it raised $100 million, including a small investment from CureDuchenne, one of six different next-generation exon-skipping approaches Debra backed after 2015.

Though still wary of other advocates, she knew Hawken and other families needed treatment. And now she had resources. BioMarin's Prosensa buyout had landed her a nifty $7 million return.

In exchange for investment, Debra pushed the companies to focus on Duchenne, alongside muscle diseases with larger markets. And though she argues that CureDuchenne spent heavily on approaches that wouldn't benefit Hawken, she also pushed for specific patients. Levin agreed to start with Hawken's mutation.

"At that point, I was like it's time," she said. "It's time."

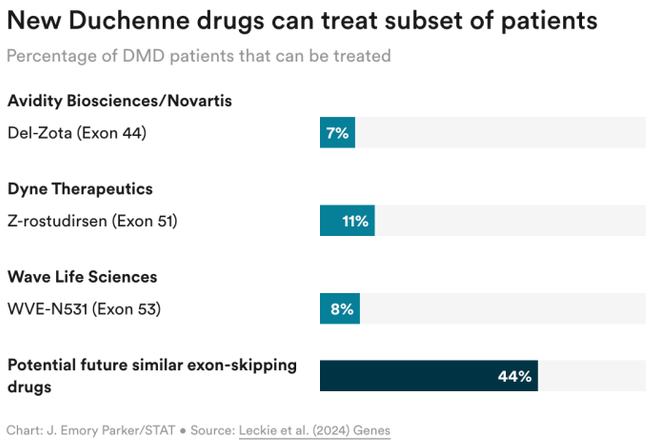
'I have seen miracles'

Hawken's doctor, Brenda Wong, poked her head into the exam room and apologized: They needed to redo the bloodwork, she said, one of the lab machines was broken.

It was June 2024, a warm day at UMass Chan Medical School. The Millers flew out every year for Hawken's physical, having adored Wong. But this checkup was different. It was the first since he had enrolled in Avidity's exon 44 skipping trial.

Hawken was 27 now, older than the textbooks said he would live. If this was a credit to a mild mutation and incrementally advancing medical care, it was also, he believed, credit to Christ.

He had lived a good life. The eighth grade essay drew him to writing. In college, he reported on immigration in Tijuana and, later, on the glitzy Overwatch video game championships for the Washington Post. His missionary work brought him purpose. He worked with youth in foster care and attended Bible studies. He thought often of Romans 8:28: "And we know that in all things God works for the good of those who love him, who have been called according to his purpose." (He had also had quite a bit of fun — attending USC Trojans football games and using his handicap pass to get to the



front of a Walk the Moon concert.)

Still, the disease was progressing. He could no longer point the Canon Rebel XTi camera that had once hung on his neck like a locket. He left journalism when he lost the stamina for long assignments, turning instead to a communications role at the company that made his wheelchair. He knew time was not infinite. Eventually, like most Duchenne patients, his heart would falter, or his lungs would give out.

He tried not to think of it much. He had his peace, even as he held out some small hope for a change. "I have seen miracles, and I have seen God heal people," he said. Sometimes, he added, God worked through scientists.

This checkup would offer the first sign of whether Avidity's drug could avert the inevitable.

Then Wong came back. The machine was fine. She just couldn't believe the result. They had measured Hawken's CK, the same test that had shredded whatever plans the Millers had for their life.

Instead of thousands, it was now 127, no higher than any person walking down the street. His remaining muscles, it seemed, were no longer crumbling. His heart, he would later learn, was healing.

He, Paul, and Debra sat there speechless.

"That's pretty miraculous," said Hawken. "If they tried to diagnose me based on that number today, I would not have Duchenne."

A glimpse of new futures

The data could not have come at a better time for the Duchenne community. For years, it seemed gene therapy, in which dystrophin is shrunken to a third of its usual size and tucked inside a virus, might halt the disease. But randomized trials yielded mixed results, and serious safety concerns, including deaths, emerged.

The boys treated with Avidity's drug have normal or near-normal CK levels and dystrophin levels, on average, of 32%. The results suggest that, in a disease marked by disintegrating muscle, for some boys "there is not ongoing muscle damage," said Kevin Flanigan, head of gene therapy at Nationwide Children's Hospital and a study investigator.

Younger patients might imagine a different future. Tyler Upchurch's two sons, 12-year-old Ezra and 10-year-old Patrick, enrolled in Aviditiy's trial two years ago, as they were beginning to lose the ability to walk. Now their CKs have flatlined and Ezra's lung capacity is 30% better than a typical healthy child's.

Recently, Upchurch e-biked with them 31 miles from their Tennessee home to Memphis, father racing sons along the beaver- and turtle-spotted waterways of Shelby Farms Park. He wonders if they'll even bring their wheelchairs the next time they travel.

"It seems too good to be true," he said.

His 3-year-old son, Nathaniel, also has Duchenne. He's calling the study team repeatedly to see how soon the toddler can get the drug, before any symptoms crop up.

Dyne Therapeutics, founded in 2017 around a similar transferrin-antibody approach, reported reaching around 5% dystrophin targeting exon 51. Wave Life Sciences, using a new kind of chemistry, reported 7.8% for exon 53. Equivalent drugs from Sarepta produce around 1% dystrophin or less.

All three companies are pushing for accelerated approval, while they launch Phase 3 trials. Like Sarepta, they may charge a fortune: Dyne CEO John Cox recently floated a $1 million per year price.

By the precedent used to approve Exondys 51, all should meet the bar. But recent turnover at the FDA, including a chaotic series of rare disease decisions, has given advocates and analysts pause.

"It's possible they will get approved," said Woodcock, the FDA official who approved Exondys 51. "But I can't predict what they are going to do."

Next may be treatments for myotonic dystrophy and facioscapulohumeral muscular dystrophy, two conditions that affect over 50,000 Americans but have no approved drugs. New data for muscle-targeted drugs from Avidity and Dyne should be available within the next year, with a slew of other companies trailing.

Those companies are similarly working to scale the approach to more patients. Upward of 60% of Duchenne patients have mutations that might be treated with exon skipping, but many of them are individually ultra-rare. New FDA guidance for individualized medicines could allow developers to redesign their exon-skippers for new patients at minimal cost.

At CureDuchenne, Debra and her team are searching for ways to boost exon skippings' or gene therapy's efficacy, while trying to ensure Dyne, Avidity, and Wave apply their technology to as many patients as possible. "Harassing might be too strong of a word," Debra said last year. "But we have been strongly encouraging."

She's also mulling retirement. She'll never leave CureDuchenne entirely, but decades ago, she imagined she'd spend her later years gardening and riding horses. Now she wonders if she finally might.

Hawken has other things on his mind. For years, he avoided dating or starting a family. He knew he might not live long. He knew that would be hard on anyone in his life. The Avidity results led to a change of heart. The search has been slow, but on a recent Zoom meeting, his mom mentioned he maybe — just maybe — may have stumbled on the right person. "We won't name names," Hawken said. "But possibly."