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HealthCare

Groundbreaking biotech gets closer to saving kids with a rare disease



Maggie Carmichael, seen here with her mother Holly, has been treated in a single-person clinical trial of epalrestat, a drug approved in Japan to treat diabetic nerve damage.

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An entrepreneurial Bay Area researcher, a Mayo Clinic doctor and a company launched by the parents of an aspiring ballerina with a rare genetic disorder could be on the cusp of reshaping the course of a rare but potentially deadly disease.

Maggie's Pearl LLC - a joint venture by Berkeley-based public benefit company Perlara and a nonprofit started by the parents of 8-year-old [Maggie Carmichael](#) - got the green light last month from the Food and Drug Administration to start a late-stage clinical trial using a drug developed 20 years ago to treat diabetic nerve damage. Researchers believe the drug could target a disorder that severely delays development, causes distinctive facial features and, in some cases, leads multiple organs to shut down.

The 40-patient study is expected to begin as early as mid-February, said Perlara founder and CEO [Ethan Perlstein](#).

"It's been a long journey," Perlstein said.

Indeed, [Perlstein Labs](#) was created eight years ago with a \$2 million stake from not-yet-infamous biotech hedge fund player [Martin Shkreli](#) as well as angel investors and a San Francisco family whose daughter had a rare disease. The idea was to tap insights from under-used yeast, worm and fruit fly models as well as genetic material from rare-disease patients to point researchers toward new or repurposed drugs.

Shkreli, who was [convicted in 2017](#) for securities fraud and conspiring to commit securities fraud on unrelated ventures, was bought out of his stake in Perlstein's venture. Meanwhile, Swiss drug giant Novartis AG, billionaire entrepreneur [Mark Cuban](#) and other investors came aboard.

The effort, which morphed into Perlara, centered on so-called "PeriQuests," essentially sponsored-research initiatives. The

PerlQuest with the Carmichael family began in 2017.

"Maggie's Pearl is the culmination of the core vision of Perlara to create a joint venture with highly motivated families or foundations that could co-develop a medicine together," Perlstein said.



Ethan Perlstein is the CEO of Perlara, a company set up to form partnerships with families and foundations aimed at rare diseases.

COURTESY OF ETHAN PERLSTEIN

Yet Perlara's ambitious effort didn't pan out as planned, and Perlstein hibernated the company in early 2019.

'You bring the dollars, I bring the brains'

The shuttering gave pause to Maggie's parents, Holly and **Dan Carmichael**. From their home in Sturgis, Michigan, and with the help of other family members, they have turned over hundreds of thousands of dollars to Perlstein over the past five years.

"You hear nightmare stories of families raising money and giving it to a researcher, and they don't get what they wanted or the company closes," said **Holly Carmichael**. "That's where the luck comes in: Ethan's a great guy. He was committed to finishing Maggie's project.

"His model is 'You bring the dollars, I bring the brains and together we'll try to find a treatment for your child,'" she said.

Maggie's project rolled on, with researchers screening drugs against yeast and worm models of the disease that are proprietary to Perlara. They found a hit for a pill approved in Japan in 1992 for diabetic neuropathy.

The disease - called PMM2-CDG, or phosphomannomutase-2-congenital disorder of glycosylation - is caused by mutations in a gene that supplies the instructions for making the PMM2 enzyme, which is involved in a process known as glycosylation. In that process, sugar chains are created, altered and chemically attached to specific proteins or fats to form glycoproteins. Those proteins are key to normal growth and function of tissues and organs.

"The enzyme is in every cell of every animal," Perlstein said, "from a single-cell yeast to humans."

The disease wasn't identified until 1980 and the gene responsible for it wasn't pinpointed until the 1990s. Even then, Perlstein said, the disease is under-diagnosed, especially in Black and brown children, and often is characterized as a "failure to thrive" in children.

When the enzyme is deficient, the right number of small sugar molecules can't link together and parts of the body don't develop as they normally would. Eyes may look in different directions, nipples can be inverted and fat pads form above the butt, for example; other patients can suffer neuromuscular problems and experience severe developmental delays.

PMM2-CDG is the most common form of glycosylation disorder - or as **Holly Carmichael** describes it, Maggie's disease is just one point where the glycosylation assembly line breaks down; other types of CDGs stop the line at other points.

Maggie's journey

By January 2020, Maggie herself pioneered a one-person trial of the daily pill, called epalrestat, under the supervision of the Mayo Clinic in Rochester, Minnesota. The results are stunning.

For one, Maggie no longer "face plants" - which had occurred a half-dozen times a day - while four-point crawling on the floor. She is more stable standing, using a gait-trainer walking device instead of a wheelchair as she pursues her dream of becoming a ballerina. She sits up in the bathtub, no longer requiring a bath seat.

What's more, her fine motor skills have improved to the point

well. It's like, we're finally getting to the point where she can feed herself and color inside the lines, and her speech skills have exploded.

Maggie's vocabulary has grown 10- to 20-fold, [Holly Carmichael](#) said, and her ability to process and respond in conversation has dramatically improved.

The Mayo Clinic has since joined on as a co-owner of Maggie's Pearl, with Perlstein as CEO and [Holly Carmichael](#) as COO.

"This is not a miracle cure," [Holly Carmichael](#) said. "We set out to find a cure; at this point, it's more of a treatment. But the quality-of-life gains have been amazing."

New trials, tribulations

After about a year of the Maggie-specific trial, Perlstein and the company the Carmichaels formed to pay for research created the Maggie's Pearl joint venture, so they could design a clinical trial with dozens of patients. Dr. [Eva Morava-Kozicz](#) at the Mayo Clinic last summer filed paperwork with the FDA to undertake a Phase II, or mid-stage, study of epalrestat for 30 patients.

The FDA, however, rejected the plan.

One patient's symptoms and characteristics can be unique to an organ or in their severity from those of another patient, even within the same family. What's more, PMM2-CDG isn't a death sentence for all of the 1,000 known patients in the United States and Europe; it can be fatal for some infants with multiple organ failure, but other patients can live to adulthood.

The FDA wanted a placebo-controlled trial that would accurately measure the drug's impact.

"I understand the scientific perspective that a placebo-controlled trial is the gold standard, but I just feel bad telling a parent that my kid got it but your kid may be on a placebo," [Holly Carmichael](#) said. "But if we can get it approved, we can get it out to everyone."

After months of negotiations with the FDA, Maggie's Pearl ended up with a late-stage, Phase III trial with two biomarkers of the disease that can be quantified by lab tests as well as a functional measure of abnormal, uncoordinated movements - a condition called ataxia - that can be measured by a doctor.

In Maggie's Pearl's favor is decades of safety data from epalrestat's use in Japan and India. That helped allow the drug's jump to a trial that, if successful, could bring it back to the FDA for an approval decision.

"If we can do this once, it could be definitive," Perlstein said.

"Then we've answered the questions about this medicine and the mechanisms more broadly, and it won't just linger on in investigator-sponsored studies."

The cost of the late-stage trial, expected to last anywhere from six months to three years before enough data arrives to make a call on its success or failure, could run \$3 million to \$5 million, [Holly Carmichael](#) said.

"It's a smaller trial, so the costs are reduced, but we still have to do the study that convinces payers, other families and researchers," Perlstein said. "You have to convince people this is not just a squint-your-eyes kind of thing."

If the results are anything like those seen with Maggie and two separate one-person trials in Canada, [Holly Carmichael](#) said, the next step would be to test epalrestat in other glycosylation disorders.

Until then, though, Maggie's Pearl principals and the company's young namesake hope to see continued discoveries.

"She's so smart and clever - and she's funny. It's been amazing," [Holly Carmichael](#) said of Maggie. "My husband said, 'We actually got to meet Maggie.'"