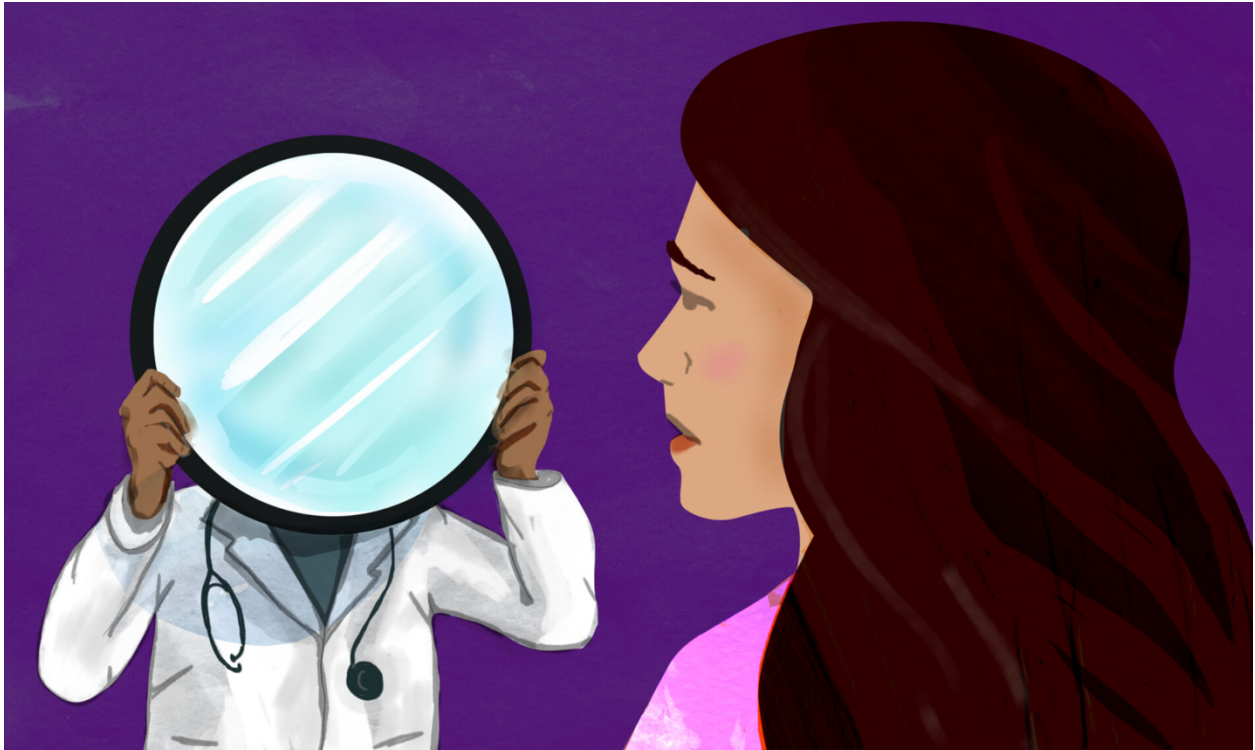


# Revenge of the gaslit patients: Now, as scientists, they're tackling Ehlers-Danlos syndromes



By [Isabella Cueto](#) Dec. 12, 2022



Type “Ehlers-Danlos syndromes” into a search engine, and multiple suggestions pop up. Is Ehlers-Danlos an autoimmune disease? Is EDS hereditary? Rare? Then, the algorithm might suggest: Is Ehlers-Danlos syndrome a disease? “Is EDS real?”

The latter is a question that really annoyed Cortney Gensemer, a postdoctoral researcher who studies and has EDS. How could people — even doctors — not believe in a group of illnesses that have inflicted tangible symptoms on her and several of her relatives? Patients might look healthy, their tests might show no signs of disease, but they endure repeated joint dislocations, headaches and pain, as well as gastrointestinal issues, fatigue, and stretchy and fragile skin. All of these symptoms are present in some forms of EDS. Gensemer has the most common of the 14 subtypes, called hypermobile EDS.

But since, unlike the other 13 types, hEDS has no known gene, it stays in medicine's gray area.

No matter. Gensemer used other people's suspicions as propellant. She hit the research bench, her gaze set firmly on this group of connective tissue disorders. "Let's publish in top journals and send them a copy and sign it — that's how I feel now," she said.

The medical gaslighting she endured as a patient? Now, it's material for her work in the lab of Russell Norris at the Department of Regenerative Medicine and Cell Biology at the Medical University of South Carolina. For four years, Gensemer has helped pry open DNA from people with her same illness to figure out what gene variants might be responsible.

She is one of a generation of young patient-researchers, mostly women, who have hEDS and are studying the disease — its genetic sources, the way connective tissues break down, how modern diagnostic tools are failing patients, and which might be more effective, and more. They are redefining what the study of chronic disease can look like by smudging the line between patient and researcher, channeling their experiences into determined, careful science. They are showing that patient-led inquiries could be indispensable in the effort to crack complex, long-misunderstood illnesses, like hEDS.

## **Revenge story No. 1: she's helping find a genetic cause**

**T**he Norris Lab didn't just go looking; researchers found a gene variant that an unknown percentage of hEDS patients could have, one that would explain their disease.

In a large family with hEDS, the lab found a pattern — genetic anomalies some members shared. Then, they found more hEDS patients with mutations, via an online registry that went gangbusters overnight in December 2020. They narrowed down to 10 gene variants, and then to one they thought might be causing disease.

From humans, the Norris Lab team went to mice, and edited the suspect gene mutation into their DNA. The mice became so hypermobile that researchers could tie their tails into small knots.

The announcement on the Norris Lab website — that they had found a promising genetic clue, though they haven't shared the name of it yet — caused such a stir in the world of EDS that Norris has had to mute his office phone. People want to know what they found, and have even submitted guesses of what gene variant is to blame. Their

findings have been submitted to a scientific journal for review. (There are other researchers searching for genetic causes, including ones at Tulane University School of Medicine, who recently submitted a paper to the journal *Heliyon* about a hypermobility gene they identified.)



Cortney Gensemer, a postdoctoral scholar at Medical University of South Carolina: “Why aren’t we seeing patient representation in the research that’s going on?” Here, she demonstrates how Russell Norris’ lab tests DNA samples of patients with hypermobile Ehlers-Danlos syndrome.

*ANDREW WHITAKER FOR STAT*

News of an hEDS gene variant is full-voicemail-level big because none has ever been linked to the disease and tested in an animal model before. Such a discovery means the possibility of a genetic test, which would prove the existence of this disease in some chunk of the patient population. It’s clear there will be more than one hEDS gene, but the Norris Lab’s discovery is an important start to that effort.

It was Gensemer, sitting in Norris’s Charleston office four years before, who told Norris that nobody had found a genetic root of hEDS. Norris was, at the time, comfortably situated as a cardiovascular geneticist with a focus on heart valve diseases. The only reason they were chatting was that Norris was a graduate coordinator (basically, a mentor) for the Ph.D. students. And the only reason EDS came up was that some of Gensemer’s family members had mitral valve prolapse as a result of their EDS.

Norris asked what gene variant she had. She told him none had been found. Incredulous, he asked Gensemer if she wanted to try to find a gene. “Sure,” she said, “We can do that?”

## Revenge story No. 2: She’s telling their stories

In the moment Melissa Martin had been preparing for, she stood over a marimba, a pair of mallets in each hand. She had already passed her final piano exam with high marks earlier in the week, despite the unreliable joints in her hands. They had only gotten more wobbly in the preceding months as she practiced her instruments for up to four hours a day. Now, all she needed to do was ace the marimba exam, and she could attend a university conservatory, and earn a double degree in piano and percussion — her dream.

But as she played the first few trilling notes of “[Etude Op. 6, #10](#)” by Clair Omar Musser, she felt so faint that she had to stop, leave the room and vomit. She went home.

Although the exam board offered to reschedule free of charge, Martin had to face her reality: “I knew that my body couldn’t do it,” she told STAT.

Martin had always been labeled a “sickly child,” she says — in and out of hospitals with various infections, her ankles prone to giving way at random. On vacation in Orlando when she was 11, Martin fell to the ground over and over as her family walked around the theme parks.

But according to doctors in Florida and back at home in Wales, she was fine. They reassured her that the leg pain was from growing, that her tests looked normal, and maybe she was just anxious. They told her parents that Martin’s increasingly common fainting spells were what “all teenage girls do.”

In secondary school, Martin struggled to walk between classes and even the basics became difficult: “I didn’t have control over the pen, which was hugely frustrating because I was really academic,” she said.

Then one day when she was 14, her podiatrist took a look at Martin’s hypermobile ankles and wrists, her growing list of problematic joints, and asked, Have you ever heard of Ehlers-Danlos Syndrome? Martin immediately asked her parents if they would buy her [a book about living with hypermobility](#). The sections on EDS resonated. “I read it and thought, ‘Maybe it is that.’” Her mum read it, and the following week booked an

appointment at a clinic in London — a six-hour drive away — that specialized in hypermobility. Twenty minutes into that visit, Martin was diagnosed with hypermobile EDS and POTS — postural orthostatic tachycardia syndrome, a circulation disorder that can cause dizziness and sometimes accompanies EDS.



Melissa Martin recalls her diagnosis with hypermobile EDS: Besides feeling devastated, she was “so, so happy to know that it wasn’t a problem with me as a person.” Shown this summer at the University of Warwick, she is now a sociologist studying EDS.  
*COURTESY JUSTIN SILEZIN*

“I was devastated in the sense that it wasn’t something that could be fixed,” she told STAT. “But also, so, so happy to know that it wasn’t a problem with me as a person. It wasn’t that I was being lazy or that I had a really rubbish pain tolerance, or that I was just overly anxious about my health — there was a genuine problem.”

When, several years later, her plan to pursue music was foiled by illness, she decided to study sociology, eventually focusing on the disease that had thwarted her instead. She’s since interviewed dozens of people with hEDS and other hypermobility-related conditions. Common themes emerge. A lot of doctors either have never heard of EDS or don’t know much about it. It takes a savvy clinician to weave together disparate symptoms, spread out across the body and invisible on most tests, and arrive at an

answer. As with many chronic conditions, symptoms can be hard to describe, and they can come and go and change over time.

It's why communities of EDS patients say, "If you can't connect the issues, think: connective tissues." It's why EDS patients have adopted a zebra as their mascot — doctors are trained to associate hoofbeats with horses, but sometimes, it's a zebra.

One gene variant, or even multiple, won't solve the many problems hEDS patients face. A bright genetic line between hEDS and other disorders could legitimize the condition in a medical context. But it could also become another Beighton Score, a hypermobility measure that's become a tool of exclusion that thwarts patients' search for answers, some argue.

Delays to diagnosis are well-known among EDS patients, in part because of inaccessible health systems. In the U.K., most specialists are concentrated in London, and often require private insurance. In the U.S., the few EDS specialists that exist often have months- or years-long waitlists, and don't take insurance.

The profound impact these problems have on people's lives often remains unseen, Martin says. One person she spoke to during her fieldwork grew up doing high-impact sports, like roller skating and rugby. They suffered injury after injury, repeated dislocations of the shoulder, knee and elbow. As the disease progressed without diagnosis, they'd dislocate a shoulder just trying to put a shirt on.

Those with anxiety disorders or other mental health struggles, which are common among people with EDS, have reported to Martin feeling doubly marginalized, and told they are overthinking or being a hypochondriac. Women, ethnic minorities and people with other stigmatized health conditions especially have reported feeling intensely dismissed and discriminated against by medical providers, Martin said.

"What often happens is that people start hating themselves, because they feel like a failure, that they can't fit into this world, that everyone's expecting them to do certain things in certain ways," she said.

Martin herself tried pushing through her EDS when she moved away from home for university in England. By the Friday of her first week, she couldn't get out of bed because her legs wouldn't hold her weight. That day, her parents drove to get her and, with Martin's friend, took her to buy a mobility scooter. Having a mobility aid opened up her world. She could go to classes without feeling constant pain and exhaustion, which let her focus on her studies and gave her back the energy to start playing music again in various university groups.

## Revenge Story No. 3: She's upending the test

Ehlers-Danlos Syndrome, or some ancient version of a disease like it, was described centuries ago. Hippocratic medical texts explained how those who are “slack in tendency” had trouble doing routine tasks, said Martin, who read translations of the documents for her research. In the late 19th and early 20th centuries, three dermatologists recognized this group of symptoms as a syndrome. The Russian doctor A.N. Tschernogubow, the Dane Edvard Ehlers, and French physician Henri-Alexandre Danlos all wrote about their findings, but the latter two had the disease named after them. Some consider EDS to be rare — estimates of prevalence are difficult — but increasingly, they are seen as common, neglected illnesses.

One of the primary tools used to diagnose hypermobile EDS is the Beighton Score, a 50-year-old physical examination that involves bending patients' fingers and other joints and rating their flexibility on a nine-point scale. A score of five or more means an adult has “generalized joint hypermobility.” But, the catch: hypermobile joints aren't, by themselves, a problem; some people are hypermobile but don't have pain or dislocations or other symptoms, and some joint plasticity can be trained and manipulated. Many people with hEDS were formerly athletes who benefited from their limberness, like dancers and gymnasts, but later developed problematic symptoms. Each patient's condition looks slightly different.

The lack of consistency means there is no clear treatment approach for hEDS patients. Medications can treat symptoms — pain, joint swelling after dislocations — and physical therapy can help some patients, but it's all a patchwork.

This is the confusing ecosystem patient-researchers inhabit. Sabeeha Malek learned about EDS and POTS online, as many patients do. During her undergraduate studies in biomedical sciences at the University of Warwick in England, Malek started developing chronic fatigue and chronic pain, vague symptoms that deteriorated into serious illness near the end of her degree. She took time off from university to try to figure out what was going on with her body. “Doctors would often tell me that nothing was wrong with me and that my symptoms were all in my head. It was very distressing to be told your pain isn't real,” she said.

At 24, she asked her rheumatologist about EDS, and he performed the Beighton Score examination. She was borderline, he told her — didn't quite meet the criteria for hypermobile EDS.

Malek reminded him that some of her other joints, those not included in the Beighton, were hypermobile. He was unsure of how to diagnose EDS outside of the criteria, Malek remembers him saying. It took a specialist to diagnose her with hEDS and tell her she was hypermobile in almost every single joint other than those measured by the Beighton Score.

With the help of medication to control her POTS symptoms and chronic pain, she was able to enroll in a master's program at Coventry University. Her focus? "All I could think about was the Beighton Score and how it had almost robbed me of a diagnosis," she told STAT.



Sabeeha Malek: "Doctors would often tell me that nothing was wrong with me and that my symptoms were all in my head." Now a doctoral student at the Centre for Mechanochemical Cell Biology at Warwick Medical School, Malek has published research challenging a common test for hEDS.

*COURTESY SABEEHA MALEK*

Malek read studies that showed how the score didn't capture hypermobility in the shoulder, hip, back, or other parts of the body. She used that research and her own experience to argue in a paper that the Beighton Score can't be used to rule out hEDS, and that doctors should also use their clinical judgment. That paper was ultimately [published as a review](#) in *Rheumatology International* — Malek's first scientific publication.

Critics of the Beighton Score see it as a case study in how unscrutinized diagnostic tools can harm patients. The score was named after researcher Peter Beighton, who in the early 1970s modified an existing scoring system, which included many body parts, to include only five easily assessed movements. Beighton and his colleagues were headed to a village northwest of Johannesburg to conduct an epidemiological study, in part due



to supposed “ethnic differences in joint mobility.” The score was used to screen a lot of people quickly, which made sense for the context, Malek says.

But the next time a researcher wanted to assess joint hypermobility, the tool turned up in the scientific literature and got used again. And again and again, lending legitimacy to what was a cursory screening method. Likewise, when clinicians had to decide what criteria to use to diagnose generalized joint hypermobility, they turned to what was established: the Beighton Score. There have been no rigorous, controlled studies formally evaluating the accuracy of the score, Malek says.

“And so I guess it’s a little bit of laziness in our research system, where we kind of just use whatever someone else has used before,” she said. “And then clinicians are left with that as their only option.”

Malek, now a doctoral student at Warwick, is something of a specialist at analyzing science in hindsight. During Covid lockdown, she couldn’t go into the lab, so she read instead. She combed through studies and took notice of cellular changes in EDS patients — mutations that the researchers couldn’t make sense of at the time, but that might explain how connective tissue becomes a problem for these patients. Malek was able to piece together those clues and draw up a [novel step-by-step process](#): how defective collagen disrupts the links between connective tissue cells and collagen, and alters how those cells behave and function. She is undertaking a proof-of-concept study to test the steps in that mechanism.

It was all there, in the papers. Someone just had to care enough to look.

## Revenge of the interns

Norris, head of the Charleston lab, began looking at EDS as a side project. He wanted more patients in order to figure out how frequent the gene variant was that he and Gensemer had found, but that was pretty much it.

Then, over the span of a few weeks, more than a thousand people responded to their call for patients. With no staff and no funding, Norris and Gensemer had to patch together a lab, hire a clinical research coordinator and figure out how to pay for their work. They got early funding from the EDS Society, and then the surprisingly large community of EDS patients throughout the country drove the charge with philanthropic funding. And a few other things happened, which moved hEDS from side to center stage in the lab.

First, Norris, who'd spent his career up to that point tucked safely in a lab, away from patients, was hearing from hundreds of them at a time. He heard the struggle, the frustration, the anger, and the hope. And then, a donor, whom Norris didn't name but who has a personal connection to the disease, called Norris and offered him \$50,000 to hire some staff. He used that money to start a 10-week summer internship program, explicitly created for burgeoning patient-researchers who have hEDS and plan to keep working in the disease.

**“Let’s take these people who really understand, who have really important questions to answer and give them the tools to learn how to answer them.”**

CORTNEY GENSEMER, POSTDOCTORAL SCHOLAR AT  
MEDICAL UNIVERSITY OF SOUTH CAROLINA

“Let’s take these people who really understand, who have really important questions to answer and give them the tools to learn how to answer them,” Gensemer said. “They already come in with ideas about things they’d like to study or projects they could potentially have in the lab. So why aren’t we seeing patient representation in the research that’s going on?”

They received 25 applications for four spots the first year. Nine interns have graduated so far from the program, which is named after Gensemer. And in no small part due to that internship program, the Norris Lab is now one of the leading research groups with a concentration on hEDS. It boasts one of the largest patient hEDS registries, over 6,000 people, 92% of whom identified as women, Norris said.

Research groups around the world are using their limited bandwidth to do “some good stuff around hEDS,” Norris said (Christina Laukaitis at the University of Illinois, Ellen Elias at Children’s Hospital Colorado and Marina Colombi at the University of Brescia, Italy, to name a few). “But there’s really no big engine that’s moving it forward.” This is his new crusade: more groups studying the disease, and more programs that engage patients as collaborators.

There are numerous other patient-researchers studying Ehlers-Danlos. Jade Barclay of The Kolling Medical Research Institute in Sydney, Australia, researches equitable access to care for people with hypermobility, including the patient voice and expertise in the full research cycle, from research design to real-world impact. “All the brochures say that research is focused on improving patient outcomes — nobody is more committed to that than patients who are living it every day,” Barclay told STAT. Sarah Hannon, a Ph.D. candidate in pharmacology and toxicology at the University of Arizona College of Pharmacy, is studying hormone levels in people with EDS, and how they align with patients’ menstrual cycles, to assess whether hormonal fluctuations are behind the higher rates of gender dysphoria in EDS populations. At Al-Razi Orthopedic and Rehabilitation Hospital in Kuwait, Najla Alsiri developed an ultrasound-based method to measure changes in tissue stiffness, which could help diagnose EDS.

## What tomorrow could look like

All of these researchers, and the many patients who aren't in labs, desire a future where EDS is recognized as a real, damaging condition — one deserving of attention and comprehensive care.

But bureaucratic barriers stand in the way.

For instance, the National Institutes of Health has never funded a research project grant in hypermobile Ehlers-Danlos Syndrome, according to [publicly available data](#). And without support from a major public funding agency, researchers are often left to scrape together resources or seek out private donations.

Norris is submitting his first R01 grant to the agency in coming months — one of many risks he's taken since that first conversation with Gensemer, four years ago.

He thinks through the possibilities: The paper with the promising gene could be rejected by journals, or take months to publish. The lab could fail at getting NIH funding. “It could be a career-killer,” Norris told STAT.



Russell Norris on the need for more hEDS researchers: “The best people who are committed to it are those who suffer from the disease or those who have family members that suffer from the disease.” His lab has caused a stir with news about a gene variant linked to hEDS.

ANDREW WHITAKER FOR STAT

He's already felt the pressure that comes with this work. Norris no longer uses social media because of the vitriol against him, the claims made by strangers that he's just in it for the money. Gensemer has faced online comments from people questioning the quality of her research ("if anything, I'm biased toward being wrong," she says), and why she hasn't developed a treatment for EDS if she's found a gene.

Martin, who's never publicly disclosed her hEDS diagnoses in her capacity as a researcher before, has struggled to handle criticism, particularly online comments, from people assuming she doesn't have EDS. But now that she's open about it, will she get the other side: those who question her motives? "I was quite frightened for a long time about the ways it might detract from my work," she said. But more and more, she sees how her experience actively adds value to her research. "Increasingly, I see that everyone brings these subjectivities to their work, whatever kind of work they're doing."

Down the road, Norris envisions an hEDS institute, a one-stop-shop that would combine full clinical care and research, and EDS centers of excellence around the country. He sees a medical school curriculum that includes more than a passing, inaccurate mention of Ehlers-Danlos, starting with the Medical University of South Carolina, where Norris will teach about the disease.

If nothing else, he hopes the internship program will outlive him. How many EDS researchers can sprout from one lab? How many can emerge from multiple? He and Gensemer want to find out.

"There have to be more people committed to it," Norris said. "And the best people who are committed to it are those who suffer from the disease or those who have family members that suffer from the disease."

For diseases like EDS, those illnesses so ignored or misunderstood that patients can barely find a knowledgeable doctor, much less the genetic source of their condition, it may require those with intimate, untapped knowledge — patients themselves — to shepherd science forward.

*STAT's coverage of chronic health issues is supported by a grant from [Bloomberg Philanthropies](#). Our [financial supporters](#) are not involved in any decisions about our journalism.*

*Get your daily dose of health and medicine every weekday with STAT's free newsletter [Morning Rounds](#). [Sign up here](#).*