

# THINK ‘ZEBRA’

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**ABSTRACT**

Thousands of rare diseases affect 300 million people globally, but a potential breakthrough in one sheds light on the systemic barriers to research and diagnosis.

Ehlers-Danlos Syndrome (EDS) has thirteen subtypes, and, to date, all but one have at least one identified genetic marker. In 2021, researchers at the Medical University of South Carolina announced they may have found the first genetic marker for Hypermobile Ehlers-Danlos Syndrome (hEDS). This subtype is the most common and is commonly believed to be less severe than other types of EDS, which is not the case. Further, recent research shows hEDS may not be rare at all, a misconception that is potentially a consequence of systemic underdiagnosis that impacts both patient lives and the flow of research funding.

Through stories of scientific research, healthcare provers, and patient experiences, this thesis illustrates the interplay between: difficulty of rare disease diagnosis, systemic barriers that prevent diagnosis, and the effects these have on institutional research into rare disease.

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**I**N 2017, a modest wedding took place on the shores of Mount Pleasant, South Carolina, a quick crow's flight across the bay from Charleston.<sup>1</sup> The temperature that late May afternoon hit the 70s,<sup>2</sup> and a few dozen people celebrated a union of families. Crashing waves accompanied notes of laughter and weeping mothers.<sup>3</sup> Julianna Weninger wore a crisp white dress, a royal blue "W" topped the wedding cake, and a coral horizon ushered in a perfect southern sunset.<sup>4</sup>

"I had kind of had in my head that I was going to be alone for the rest of my life," Weninger recalled. "Who is going to want to put up with this?"<sup>5</sup>

When she was 13, Weninger was diagnosed with Ehlers-Danlos syndrome (EDS), a rare disease<sup>6</sup> that affects the body's connective tissues, which bind and support other tissues in the body.<sup>7</sup> EDS has fourteen subtypes, and, in many of them,<sup>8</sup> the body has a faulty recipe for producing collagen or another vital structural protein. There are several kinds of collagen, but generally, these tough, rigid proteins provide structure and support to connective tissues. For people with EDS, mutations in genes associated with collagen production prevent the proteins from being assembled properly. The ingredients to make collagen are there, but bad instructions mean defective proteins.<sup>9</sup>

Tendons, ligaments, and skin are all connective tissues,<sup>10</sup> and a quick search for photos of people with EDS will show fingers bent backwards and skin stretched wildly. This ability to bend joints to extreme ranges, known as hypermobility<sup>11</sup>, is a hallmark of EDS<sup>12</sup> — contortionists often have the disease, as do dancers and gymnasts.<sup>13</sup> But blood, bone, fat, lymph, and cartilage are also connective tissues,<sup>14</sup> which means that EDS is often a painful, multisystem disease that can cause a range of problems, including chronic pain, digestive issues, and deadly heart conditions.<sup>15</sup>

For Weninger, who had hypermobile EDS (hEDS), the disease was incredibly disabling. Like others with hEDS, she had problems with her heart, nervous system, and immune system. Managing the disease meant regular medical appointments along with frequent and unexpected surgical procedures. By the day of her wedding, Weninger, 23, had already had two dozen surgeries.<sup>16</sup> Her neurosurgeon, Dr. Sunil Patel, was among the ceremony's attendees. "I was tearful that day," he recalled.<sup>17</sup>

Officially, EDS is estimated to affect about 1 in 5,000 people.<sup>18</sup> It takes, on average, over a decade to diagnose. The systemic and socioeconomic barriers to diagnosis are significant, ranging from a lack of health insurance to the dismissive attitudes and discriminatory practices that are all too common among healthcare workers. Navigating the healthcare system can be complicated and time-consuming. And while there are now simple diagnostic checklists for EDS, many clinicians don't even know the disease exists. By the time many people are diagnosed, their health has severely declined.<sup>19</sup>

But EDS is just one of thousands of "rare diseases," a label that generally applies to conditions

that affect fewer than 1 in 2,000 people.<sup>20</sup> And the problem of delayed diagnosis is ubiquitous. A years-long search for an explanation for chronic pain, fatigue and dozens of disruptive symptoms is standard. It takes about seven years, on average, to diagnose a rare disease, and research shows that this delayed diagnosis can cause organ damage, reduced quality of life, and increased healthcare costs.<sup>21</sup>

As the old medical school adage goes, “When you hear hoofbeats behind you, don’t expect to see a zebra.” It’s another way of saying that when someone is sick, doctors should assume the cause is a common illness, rather than a rare one.<sup>22</sup> But, according to the National Organization for Rare Disorders (NORD), the fact that medical students are often taught to focus on common diseases is a problem. Most of the barriers to diagnosis are rooted in a lack of rare disease knowledge among healthcare providers, the organization says.<sup>23</sup> To underscore this problem, the logo for the EDS Society is a zebra, and many EDS patients call themselves zebras.<sup>24</sup>

Meanwhile the term “rare” is misleading. Collectively, at least 300 million people around the world live with a rare disease, and about 1 in 10 people in the United States have one.<sup>25</sup> Some are indeed so uncommon that winning the lottery is more likely,<sup>26</sup> while others are as probable as finding a four-leaf clover.<sup>27</sup>

The majority of rare diseases are thought to be caused by genetic mutations.<sup>28</sup> Considering recent advancements in human genetics and genomics, rare disease diagnosis could, in theory, be relatively easy: Simply test patients for the mutations associated with various diseases. In reality, however, waitlists for genetic counselors can sometimes stretch for years. And a systemic lack of research funding and knowledge continues to pose major barriers to diagnosis. The genetic markers for many rare diseases remain unknown, and identifying them is just the first step.<sup>29</sup> The quest to find an hEDS marker illustrates the hurdles and barriers that remain — and what’s at stake for patients.

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Of all the EDS subtypes, most research dollars have been routed to a handful of consistently severe types, like classical EDS, which is sometimes associated with weak organs, and vascular EDS, which has a median life expectancy of 48 years.<sup>30</sup> Hypermobility EDS, the most common subtype,<sup>31</sup> has generally been considered mild.<sup>32</sup> But for some patients, like Weninger, hEDS can be terrifying.

By the time she was 17 years old, Weninger was experiencing continual spinal fluid leaks due to a defect in her spinal tissue. In 2011, she had a hollow tube called a shunt placed in the brain<sup>33</sup> to help drain cerebrospinal fluid, which cushions the brain and spinal cord<sup>34</sup>, and relieve the pressure. But the shunt soon began to malfunction, and over the years that followed, Weninger developed idiopathic intracranial hypertension, an increased pressure in the brain that has been

linked to EDS.<sup>35</sup> She experienced migraines, nausea, and vision problems.<sup>36</sup>

In January 2018, just a few months into her marriage, Weninger had surgery, her 25th, to correct the problem. The procedure, conducted at the Medical University of South Carolina (MUSC), seemed to go fine, but she soon developed excruciating head and neck pain. She recognized the symptoms as those of a brain bleed, which she had once before. Her doctors insisted she was fine. She insisted she was not, and imaging eventually revealed the hemorrhage she expected: Blood had begun to seep into her cerebrospinal fluid. She was rushed back into surgery.<sup>37</sup>

Soon, however, a new crisis hit. Weninger had been taken off the blood thinners she normally took for a clotting disorder, another common EDS complication.<sup>38</sup> Clots soon formed in blood vessels from her heart to her head, stopping blood flow to her brain, and over the next few weeks, a combination of complications sent her to the intensive care unit (ICU) repeatedly. Her upper body swelled so much she couldn't move her arms.<sup>39</sup> She had trouble breathing, her eyes pointed in different directions, and she lost the ability to tell time. Her husband brought their first Valentine's Day dinner to the ICU.

Later scans revealed that a ventricle — a brain cavity that contains cerebrospinal fluid — had collapsed. As excess fluid accumulated, an increase in pressure began to push her brain out of place, a deadly condition known as brain herniation. Most of her doctors said there was nothing else they could do. Weninger began receiving hospice care, and her family prepared to say goodbye.<sup>40</sup>

"I remember just an incredibly profound sense of sadness and disbelief and emptiness," said Tamara Bowman, Weninger's mother and a nurse practitioner.<sup>41</sup>

But Patel, the head of neurosurgical team, refused to give up. He assembled a team of specialists and asked them to imagine that Weninger was the only patient in the hospital, just for an hour or two. "Let's all put our minds together and sort it out," he said. So, they came up with a plan: They would perform a delicate surgery to place a new shunt while she was still on anticoagulants, putting her at greater risk for another brain bleed.<sup>42</sup>

For Weninger, among the fuzzy memories of that time, a few moments are vivid. Toward the end of her 55-day stretch in the hospital, Patel pulled a chair up beside her bed and sat with her through the early hours of the morning, she recalled. "Jules, I don't know if I can fix this, and I don't know if it's going to work," he told her.

Even if they succeeded in placing the shunt, he wasn't sure they would ever be able to get her off the ventilator after surgery. "But if you want me to try, I'll try to fix this," he said. Yes, if she were going to die, Weninger told him, she would go down fighting.<sup>43</sup> Weninger went under anesthesia knowing she might not wake up again.<sup>44</sup> But against the odds, the surgery went "like clockwork," Patel said.<sup>45</sup> Two days later, Weninger went home and began to recover. "That was

the worst she's ever been," Bowman recalled recently. "It's a miracle she's alive."<sup>46</sup>

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Patel has been working as a neurosurgeon and researcher for decades. "People call me an expert in EDS, but the reality is, I just happen to see a lot of patients with EDS and spinal problems," he said. There is no EDS training program, he noted; his only education on the disease was a three-sentence paragraph in a medical school textbook.

But over the course of his career, he'd noticed a pattern of failed operations in patients with symptoms of Chiari malformation, a structural problem that causes part of the brain to bulge through base of the skull. It has a variety of causes but is a common comorbidity of EDS.<sup>47</sup> Dr. Patel noticed that many of the patients who had poor outcomes after surgery to correct the problem also had EDS. "I don't like failures, and I don't like to miss anything," he said. So, he started learning more about EDS — and how to help the patients who had it.<sup>48</sup>

"These patients would have real symptoms, and standard approaches or diagnostic things never show anything," Patel said. "They're very smart, functional human beings with real problems that are impairing and disabling."

By sheer coincidence, Bowman, Weninger's mother, worked at MUSC with Patel. The two had been colleagues since Weninger was a seemingly healthy child.<sup>49</sup>

Weninger had been a competitive dancer beginning at age five. But as she got older, she began to have regular sprains and dislocations, and, eventually, frequent hospital visits for debilitating headaches. Because of her soft, stretchy skin, inserting an IV was difficult and often required the help of the anesthesiologists. Two weeks before her first surgery, to correct a spinal fluid leak, an anesthesiologist asked Bowman an unexpected question: Did her daughter bruise in a line? She did. The doctor said that he thought Weninger had a connective tissue disorder.<sup>50</sup>

Records of patients with EDS-like symptoms date back to the mid-1600s, but it wasn't until the early 20th century that the picture became clearer. Edvard Ehlers, a Danish dermatologist, and Henri-Alexandra Danlos, a French physician, separately published papers describing the condition.<sup>51</sup> Within a few decades, researchers recognized that EDS was a heritable condition, and in the early 2000s, when genetic sequencing became cheaper and faster, gene mutations associated with EDS were identified. Today, mutations in at least 20 different genes have been linked to the disorder, but scientists suspect that more are out there.<sup>52</sup>

When Bowman began investigating connective tissue disorders, she wondered whether her daughter might have EDS, but Patel was skeptical, noting its rarity. That is, until he operated on Weninger for the first time. Her spinal dura, typically a tough layer surrounding the spinal cord, was more like tissue paper. Patel had never seen anything like it. After that, Patel encouraged Bowman to seek a diagnosis for her daughter.<sup>53</sup>

Bowman began reading extensively about EDS. “I had an advantage,” she said. “I knew how to navigate a system and knew how to talk to health insurance providers.”

She brought reams of articles to appointments in hopes that some medical student or resident would be interested enough to take on her daughter’s complicated case. Within a few months, Weninger was diagnosed with classical EDS. At the time, however, no genetic test was available for most types of EDS, so Weninger’s diagnosis had been based on a clinical checklist.<sup>54</sup> These checklists are subjective, asking clinicians to tick through various physical symptoms, like joint hypermobility and “velvety” skin, that are open to interpretation and prone to misidentification. It’s easy to get the diagnosis wrong.<sup>55</sup> And as Weninger became sicker, her parents became concerned she might have the deadlier vascular EDS.

“I think as a culture, we tend to accept what the doctor says as gospel,” Bowman said. “It’s a tenuous tightrope that you walk as a parent, to not alienate the people who are providing care for your child while still trying to advocate.” At one point, she said, she was told by her employer that if she didn’t like the care Weninger was getting, she could take her somewhere else.

So she did. For two years, Bowman and Weninger traveled across the country looking for specialists familiar with EDS. Finally, in 2009, a leading EDS expert in Baltimore conducted a thorough clinical evaluation and diagnosed Weninger with hEDS.<sup>56</sup>

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**DURING** the fall of 2018, Cortney Gensemer started grad school at MUSC, just a short walk from downtown Charleston. She wasn’t yet sure of her research focus.

It didn’t take long to find it. She soon met Russel “Chip” Norris, a professor in the department of regenerative medicine and cell biology. She felt lost and wanted guidance, something Norris had offered to students at orientation. In his office, he began telling her about his research on a heart valve disease — mitral valve prolapse. Her ears perked up, and she let out a knowing, “Oh!”

“Do you know what that is?” he asked.

“I do,” she said. “People in my family have mitral valve prolapse, as part of Ehlers-Danlos syndrome.”

He was familiar with the disease generally, but he didn’t know how severely it affected people, nor how often it occurred. “It wasn’t on my radar,” Norris recalled.<sup>57</sup>

That’s not surprising. In 2019, the entire spectrum of “rare diseases” — of which there are thousands — received about \$6 billion in research funding from the National Institutes of Health. For comparison, Parkinson’s Disease received more than \$52 billion. None of it went specifically to EDS.<sup>58</sup>

Gensemer had been an athlete her whole life and joined the lacrosse team in college. But



during her freshman year, she kept getting injured. She had unusual, persistent injuries rarely seen in someone so young. First, she tore the cartilage in her hips, and then the simple act of using crutches injured her shoulder blade. At age 19, barely able to walk, she had hip surgery. She thought she would soon be back on the field.

That never happened. While using crutches after her surgery, she re-injured her shoulder.

At the time, Gensemer, who was on the pre-med track, was interning at a doctor's office. One of the doctors she worked for told her that her string of strange injuries wasn't normal and started asking bizarre questions like, "Can you touch your thumb to your forearm?" She could. The doctor, whose wife happened to have a connective tissue disorder, suggested Gensemer might have EDS and referred her to a rheumatologist familiar with the disorder, a stroke of luck.

About two weeks later, Gensemer was diagnosed with EDS, as was her father. She quit lacrosse, grateful that the doctor had said something. That diagnosis helped her realize how to take care of her body, a reason many people seek diagnosis — to get answers that can help them lead healthier, happier lives. "I couldn't imagine the shape my body would be in now," if she hadn't quit lacrosse, she said.

For many people, experiencing multiple injuries, giving up a beloved sport, and having hip surgery at 19 might sound like a distressing experience. Gensemer now thinks of her diagnosis as a relatively straightforward one, though.

"I always feel somewhat guilty when I share my diagnosis journey, because I find it very easy compared to what a lot of EDS patients go through," she said. "I've had like the exact opposite experience of everyone else." Yet, as with Weninger, the stars had to align just so for someone to see her symptoms for what they were.<sup>59</sup>

When Norris heard that Gensemer had EDS, he asked a seemingly normal question: "What's your gene mutation?"

She explained she had hEDS, which has no known genetic marker. Norris asked if she wanted to find it. She hadn't ever thought that researching her own disease would be possible, given that so few people are studying EDS. She jumped at Norris's offer, and so they set to work.<sup>60</sup>

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To begin the search, they had to look for unique gene mutations in people diagnosed with hEDS. They started with two distant cousins, both diagnosed with hEDS, and, eventually, seven more members of that extended, multigenerational family.<sup>61</sup> "After consulting with my genetics colleagues, who are some of the most established geneticists in the world, they took a look at the pedigree and said, 'Good luck,'" Norris said. "A lot of people have tried to find a gene for EDS, and they've had hundreds of samples. We have two."<sup>62</sup>

Because they are related, the same mutation is likely the cause of hEDS in the family

members. So, in 2019, the members of the family provided samples of their saliva, which were sent off to a lab for DNA sequencing. Once the researchers had the results, they looked for unique mutations the family shared, narrowing down the possibilities to mutations in just a few genes.<sup>63</sup> One seemed especially promising, due to its connection to collagen. The researchers are referring to the gene as “X” until their results are public.<sup>64</sup>

To determine whether they were on the right track, they decided to create animal models that had the same mutation in X that they had found in the family.<sup>65</sup> They started, in the summer of 2020, by gene editing mouse embryos, essentially using molecular scissors to cut, then paste, the mutation into the rodents’ genomes. But because DNA likes to repair itself, gene editing often results in extraneous mutations, which scientists using animal models have to painstakingly breed out. Eventually, after many months, they had their mouse. It was a perfectly normal mouse, other than a mutation on the suspect gene.<sup>66</sup>

Then, they examined the mice to see if they had signs of hEDS. “I was doing dissections all the time,” Gensemer said. “I was doing a lot of immunohistochemistry, western blots, things like that.” Things like that.<sup>67</sup> Western blotting is a classic laboratory technique in which scientists use antibodies to detect specific proteins in a blood or tissue sample. Performing the blots is a tedious process that takes at least a day.<sup>68</sup> Gensemer and her colleagues did hundreds, if not thousands, of them to determine whether the mutations they’d inserted in X had resulted in defects in the associated protein.

The work didn’t always go as planned. Because of the limited research on the gene family they were studying, it took quite some time to find the right antibodies. Then the company that supplied the antibodies stopped making them.<sup>69</sup> It was just one of many hiccups the team experienced while trying to find answers. Hurdles are part of science, but they are especially common in rare disease research. There are no online forums with answers, and even EDS experts are still foggy about the mechanisms of the disease.<sup>70</sup>

But the researchers kept at it, and their suspicions were repeatedly confirmed.<sup>71</sup> The gene-edited mouse, which the researchers typically picked up by the tail, was exceedingly flexible. “It was so bendy that it was able to turn all the way around and bite,” Gensemer said.

The mice have connective tissue problems with collagen,<sup>72</sup> Gensemer and Norris said, but it’s more than that. They actually show signs of one of the most common problems associated with all types of EDS: mast cell activation.<sup>73</sup> Mast cells are blood cells that play a major role in the body’s immune response. When they overreact, they can release large amounts of compounds known as histamines, which trigger allergic reactions. People with mast cell activation syndrome (MCAS) can experience allergic reactions without a clear cause; infections, medications, fragrances, food, and even exercise can all trigger these responses.<sup>74</sup>

Together, the hypermobility and mast cell activation provided strong evidence that mutations

in gene X could cause symptoms that looked a lot like hEDS, at least in lab mice.

But a big question remained: Would this mutation show up in a general population of people with hEDS? To find out, the researchers started the first clinical registry of hEDS patients. People who have been diagnosed with hEDS can sign up to participate, answering questions about their symptoms and other related diagnoses they might have, including MCAS and Chiari malformation. Patients also submit saliva samples, which are sent off for sequencing.

This new registry was a literal overnight success. Within a single day, Norris said, they had more than 1,000 volunteers. “There was a huge amount of people who one wanted somebody to work on it.”

Norris gets hundreds of emails from patients who have joined the registry and want to know what the lab work revealed about their own gene mutations. “I can tell them that we’re working on science,” he said. He can’t say much else, though. “We’re not allowed to disclose, even for people in the registry.” The samples are de-identified to protect patient privacy, and there are ethical concerns about whether to share information about other genetic mutations they might find in the samples, such as those that might be associated with cancer risk.

Even when the research is published, patients should understand that the data comes from a small sample of the hEDS population, Norris noted. And even if someone doesn’t have a mutation in gene X, it doesn’t mean they don’t have hEDS. “Your clinical diagnosis isn’t going to change,” he said.<sup>75</sup>

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**O**N October 8, 2019, I got up, got ready for work, and joined my partner on our drive down South Boulder Road in Boulder, Colorado. My muscles were aching, and there was a twinge of pain in my upper back, but I still had something to prove at my new job and had no sick leave. But as we crossed under highway 36, nearing the scenic foothills, something shifted. A storm of pain began building, rumbling through my body; the nucleus sat between my shoulder blades, slightly to the left of my spine. “Turn around,” I told my partner breathlessly. “I have to go home.” Every movement, every breath made it worse. Each pain-induced sob caused me to cry out.

I had started experiencing these episodes several years prior, while milder joint and muscle pain had begun a decade earlier. Doctors told me it was carpal tunnel syndrome, and that I just needed ice, rest and perhaps a career change. But this incident was the worst so far, and it scared me. That night, my partner had to help me into bed. He wrapped me in his arms and laid me down gently, doing his best to move in a slow, deliberate way. Still, I cried out in pain. It scared him too. He helped me get in to see an orthopedic specialist, who ordered an MRI. When I followed up with the doctor, she said that the imaging suggested I should be “fine.” I knew I

wasn't, and yet, self-doubt continued to needle — “Am I imagining it?”

I began to search for a diagnosis in earnest. Something was wrong, and I needed to understand what it was. I pored over journal articles and medical texts. At various points, I felt certain I'd cracked it — an autoimmune disease, cancer, multiple sclerosis. I saw a neurologist who ordered an MRI of my brain, which filled me with dread. I stared at the images for hours, trying to find a hint of a clue. Nothing. Blood work consistently came back normal, other than a mild b-vitamin deficiency. A highly rated rheumatologist told me to lose weight. I didn't have the energy to tell him these issues started 30 pounds prior.

I went to my primary doctor, frustrated by the lack of answers. I teared up and handed her my pages of notes — a full timeline and detailed description of all my symptoms. “Well, what do you want?” she asked. I didn't know. I needed someone to steer me in the right direction. Once, on a neurosurgeon's website, I found a lengthy list of words used to describe pain. I went through each one, checking the definition and assigning it to various experiences I'd had. Surely, if I could only communicate better with my doctors, they could help me, I thought.<sup>76</sup>

In March 2021, I decided to give one more specialist a try.

“Are you hypermobile?” Alex Reish, an osteopath in Boulder, Colorado, asked me two hours into our 90-minute appointment, after commending me on my organization and notes.

“Yes,” I told him. He went through the Beighton test, which is often used to assess hypermobility, just to be sure. “Is it EDS?” I asked.

“Maybe,” he replied, suggesting I seek genetic testing.

<sup>77</sup>Over the next few months, I found online EDS communities overflowing with information. Suddenly, I had entered a land of other sickly citizens and marveled at the sight of myself in them. An acquaintance, who lived just down the road, had also recently been diagnosed with EDS. She said part of the reason her diagnosis took so long was because she didn't pass the Beighton test. She had even been part of a study on the test's limitations.

The study noted that the test was originally intended as a screening tool and that joint mobility tends to decrease with age, even among the hypermobile population. Since even providers familiar with EDS may not fully understand the disease, using only the Beighton score to diagnose it risks missing patients altogether, the paper argues.<sup>78</sup>

In June, 2021, I had a virtual appointment with a genetic counselor at the Mayo Clinic in Arizona. My steadily increasing pain and range of symptoms had me worried. I had to explicitly ask her to go through the diagnostic checklist for EDS, which she did, briefly, and for genetic testing. She ordered the test.

A few weeks later, I learned that one of my two FKBP14 genes was mutated, making me a carrier for what is known as kyphoscoliotic EDS, or kEDS. But I only had one copy of that mutated gene and a kEDS diagnosis typically requires two. The genetic testing thus ruled out

every subtype of EDS with a known genetic marker. That left me with a diagnosis of hEDS, the only subtype without one. However, I'm uncertain that the one kEDS mutation is a coincidence, and there is a lot about EDS that scientists still don't know. So, even now, while I am confident I am a citizen of the EDS nation, I am not completely sure of which state.

While these may seem like minor details, they are critical, not only for my own health, but also for that of future generations. I now face the reality that pregnancy involves greater odds of complications, and that even if I were successful, it would likely result in greater general pain — something many women with EDS report after having children. Still, based on current evidence, as long as my partner doesn't have the FKBP14 mutation, it is wildly unlikely that we would pass kEDS on to our children.

But based on how symptoms are inherited, researchers know that hypermobile EDS is considered autosomal dominant, which means that it only takes one copy of a mutated gene to pass it on. That means there is at least a 50% chance that my child would inherit it, regardless of my partner's genetic makeup. Further, some suspect that symptoms of EDS get worse in subsequent generations, a phenomenon known as “anticipation.” If that proved true, not only would I risk my children having this disruptive, painful disease, it might even be worse for them.

While I have had to grieve this new reality, knowing that I have some type of EDS has helped me care for myself appropriately. I stopped exercising in harmful ways — yoga and jogging are contraindicated — and learned what qualifications to look for in a physical therapist. Perhaps more significantly, it helped explain the range of baffling symptoms I'd been experiencing, like the minor allergic reactions to things that hadn't previously bothered me and a newly out-of-control heart rate whenever I sat up. It even validated my neurological symptoms. Months earlier, I had been diagnosed with attention deficit hyperactive disorder, a condition that is four times more common in EDS patients than in the general population. I had also suspected autism spectrum disorder, which research suggests is about six times more likely to occur among EDS patients.

Beyond the practical benefits, diagnosis also brought me a little peace. I wasn't imagining my worsening symptoms, an accusation that dogs many people with rare diseases. This validation was its own kind of salve, as was my new perspective. For much of my adult life, I lamented that I hadn't been a dancer or gymnast while growing up home-schooled. Realizing that these pursuits could have hurt someone with hEDS helped me understand that I likely got a few more years of a seemingly healthy body.

When I was diagnosed in June 2021, hEDS was still the only type of EDS with no genetic marker.<sup>79</sup> About a month later, Gensemer and her colleagues announced that they were close to identifying one.<sup>80</sup> Later that year, I joined MUSC's hEDS registry. I would soon be visiting their lab and, eventually, adding my own saliva to the hundreds of samples they had received.

AT the Medical University of South Carolina, the southern winter sun shone through the sixth-floor windows onto sand and ivory floor tiles. Cornflower blue walls made the room reminiscent of South Carolina beaches. Papers and trinkets were scattered over desks and walls. Lab tables were cluttered with reagents, a library of beakers, and the occasional centrifuge.

I first met Weninger here, in late January of 2022, as she cleaned a counter during her afternoon volunteer shift in the Norris lab. She had started volunteering soon after the hEDS gene discovery announcement in July 2021, but she had met Gensemer years earlier at physical therapy. Some days she helps clean and organize the lab. Others she works on the budget. “Being here at the Norris lab makes me happy,” Weninger said.

Down the hall, Gensemer and her lab mates sat around a tiny table in a fluorescent-lit break area. Gensemer was scheduled to have her second spinal fusion surgery the next day. The surgery was to treat her cranio-cervical instability, another common issue among EDS patients that involves excessive movement of vertebrae where the spine meets the skull, causing neurological symptoms like headaches, nausea, and even paralysis. Gensemer’s first surgery didn’t stick, something she plans to investigate, as it seems to be a trend among EDS patients. The reasons are unclear, but it could be related to the fact that EDS patients tend to heal poorly after injuries because of their fragile tissues and tendency to bleed more easily. This kind of lived experience, Gensemer said, is another reason that patients are crucial to better understanding the disease.

As for the genetic marker, the scientists plan to submit their findings to a research journal soon. As they study more saliva samples from the hEDS registry participants, the prevalence and significance of the marker should become clearer. “This is the beginning,” Norris said. “I’m really hoping that this will catalyze and accelerate discoveries on Ehlers-Danlos.”

Later, as Gensemer sped through implications of this work, the air hummed with her passion. “With a lot of basic science, the impact, the significance of the research sort of gets lost,” she said. “We’re doing biomedical science because we want this to be translational and go back to the clinic.”

It’s still too early to say whether doctors will be able to use the marker for diagnostic testing, but that’s the ultimate goal. “Diagnosis is huge,” Gensemer said. Identifying a genetic cause for the disease also means a clearer path for developing treatments. Gene editing and gene therapy, in which the mutated gene might be permanently altered, have potential, Gensemer thinks. However, because the function of many EDS-associated genes is either complex or unclear, it’s hard to say if gene therapy is possible. Still, she said, there are other avenues worth exploring once the genetics of the disease are better understood, such as enzyme replacement therapy — a way to replace faulty proteins.

Finding genetic causes of hEDS also provides tangible evidence that the disease is real, Norris said, which could help attract more attention and funding. “It’s not viewed as really a disease by

most,” he said. “Physicians are not educated on it, so it doesn’t become a priority.”

He said someone in the registry told their team that a rheumatologist told her hEDS isn’t a disorder, but a characteristic, such as having blue eyes. “I mean, come on. You got to do better than that,” he said. “I don’t know how you guys do it after being dismissed by so many physicians.”

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To advance research and improve access to care, the MUSC team is hoping to launch an EDS institute at the university. Norris said he wants it to be a multidisciplinary, one-stop-shop for patients, with a range of in-house specialists who can treat a diverse array of EDS symptoms — gastrointestinal issues, joint pain, cranio-cervical instability, mast cell activation syndrome, and more. A dermatology student studying how skin heals could share their findings, in real time, with someone working on skeletal problems in healing bones.

While finding a genetic marker for hEDS would be an historic milestone, genetic testing is not the only way to provide a more objective clinical diagnosis. For example, doctors can diagnose some autoimmune diseases, such as lupus and rheumatoid arthritis, by looking in the blood for autoantibodies, or antibodies that attack one’s own tissues. EDS is not an autoimmune disease, but Gensemer hopes that, at some point, scientists can identify other specific biomarkers that might allow for closer-to-empirical tests for EDS.

Even developing a more objective diagnostic test is no silver bullet. It would not eliminate the rest of the diagnostic labyrinth that patients must navigate, often on their own and in the face of impossible barriers: Affordable access to healthcare, finding a doctor who knows to test in the first place, and so on. And the MUSC team’s years of work has been to find just one marker for one form of one rare disease. Significantly more research is needed for the entire gamut of rare diseases.

But research depends on funding, which often depends on interest, leaving rare disease researchers fighting over an inadequate pot of money. “Not everybody can just drop what they’re doing and work on a rare disease,” Norris said. “There needs to be some additional mechanisms to make that possible.” To that end, Norris is part of South Carolina’s newly formed Rare Disease Advocacy Council, a group devoted to lobbying for dedicated rare disease research funding.<sup>81</sup> Twenty-one states currently have these councils, but all 50 should, Norris said. With government funding limited, money for research increasingly comes from corporations and non-profits. In 2019, the EDS Society awarded around \$344,000 to various research groups.<sup>82</sup>

The inequity in funding, Norris said, leads scientists to focus on more widely known issues. But is it a self-fulfilling prophecy? EDS is said to be rare, so there is less funding for it, but less funding may mean less awareness and therefore less diagnosis. A study of over 6,000 people in Wales revealed that as many as 1 in 500 people may have hEDS or hypermobility spectrum

disorder (HSD), which is a condition with similar symptoms to hEDS.<sup>83</sup> Norris doesn't see EDS as a rare disease anymore. "We call it an uncommon disease," he said.

It's prevalent enough that even some of Norris' family have been affected, something he didn't learn about until Gensemer joined his lab.<sup>84</sup>

The walls of Norris's office are covered with his children's artwork. Across from his desk is a picture his daughter painted when she was six. His stick-figure portrait features three teeth and three strands of hair. It's just a great picture, he said. It keeps him humble.

I asked Norris what he hopes the impact of the research will be. Gensemer and her cohort will change the landscape of hEDS awareness, diagnosis, and treatment around the world, he said. "Honestly, without her, none of this would have happened," he said.

But he acknowledged that he may not be around long enough to see all the research bear fruit. "Cortney is going to be part of the wave that develops therapies," Norris said. "I'll be gone by then." As he gets older, he said, he just hopes his legacy includes changing the way people think about rare disease.

He turned away and leaned over against the window of the dim, gray conference room. A brief sound, something between a laugh and sob, escaped him. Sorry, he said. He's just an emotional guy.

The EDS research has had a different kind of impact on him than his work on other conditions, he said: "They weren't as debilitating. They didn't affect kids."<sup>85</sup>

When Weninger was a kid, she was a social butterfly. Until her diagnosis. "It's been really hard to see that change," Bowman said. "And every once in a while, when the pain isn't so bad, we see a glimpse of who she used to be. And that's wonderful, but it's also kind of bittersweet."

Weninger, who is glad to be a part of the research, often questions what an earlier diagnosis would have meant for her. Diagnosis, she said, can help people protect their bodies, especially because EDS can often cause a cascade of injuries. If she hadn't been dancing, she sometimes wonders, would she have ever had a spinal fluid leak? She doesn't know. She is open about her experiences to raise awareness. "It's worth it," she said. She hopes her story can help other people find hope, or — if the fates, medical system, and research allow — even get diagnosed.<sup>86</sup>



## NOTES

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- 40 “She had trouble...” — Screenshot of Julianna Weninger Facebook post from May 2018 describing the events of her stay in the hospital.
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