When the Illness Is a Mystery, Patients Turn to These Detectives

The Undiagnosed Diseases Network takes on the toughest cases, patients whose symptoms have defied explanation.

Sara Mason-Silva suffers from a condition in which blood vessels become blocked and inflamed, causing intense, chronic burning pain in her hands and feet. Doctors have not been able to identify the underlying cause of the disease and there is no cure. *Bryan Meltz for The New York Times*

By Gina Kolata
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They are patients with diseases that mystify doctors, people whose symptoms are dismissed as psychosomatic, who have been given misdiagnosis upon misdiagnosis.

They have confounded experts and have exhausted every hope save one. And so they wind up in the Undiagnosed Diseases Network, a federally funded project that now includes 12 clinical centers, including one at the National Institutes of Health in Bethesda, Md.

Researchers in the network pursue every possible clue — gleaned from genetics, imaging, biochemistry, clinical exams — to discover what is wrong with these patients.

In a recent study, 1,519 patients were referred to the network, but less than half were accepted for intensive evaluation at no charge. The network completed evaluations of 382 participants and found a diagnosis for 132 of them. (In the time since the study ended, the investigators have diagnosed another 128 patients.)

For some, there was good news: a treatment, often a drug that was already on the market for another condition.

Yet even patients who come away with a diagnosis but without a treatment, say the experience can be rewarding.

“Patients find it really valuable even just to give a name to the enemy,” said Dr. Euan Ashley, a geneticist at Stanford University and co-director of the network.

Those who come away without a diagnosis or treatment are told that if the science improves and an answer for them emerges, the network will contact them.

“We never give up,” Dr. Ashley said.

Here are three patients who have been through a diagnostic marathon few can imagine.

She seemed drunk, but she was cold sober

Julia Rendleman for The New York Times

Dee Reynolds, 60. Northern Virginia.

The symptoms: They began in 2005 and slowly got worse. Her speech slurred, she began weaving when she walked. Her sense of balance was precarious.

Year after year, Ms. Reynolds sought an answer, visiting doctor after doctor, getting test after test, including gene sequencing. But no one could figure out what was wrong.

Intensive testing: In 2018, she was accepted into the Undiagnosed Diseases Network.

“I had a year’s worth of testing in four days,” she recalled. “The first day was 25 vials of blood.” She had a skin biopsy, an MRI, psychological exams and eye exams. Doctors sequenced not just her genes, but the nearby regions of DNA that control them.

The diagnosis: Ms. Reynolds has an inherited disease that almost invariably occurs in childhood: Niemann-Pick Type C. The typical patient is a child who develops difficulties with walking and coordination.

The fundamental problem is a steady accumulation of cholesterol and other lipids inside the body’s cells, which damages organs and the central nervous system. The disease

progresses relentlessly to include seizures and dementia. Typically young patients die of aspiration pneumonia within a decade.

To get the disease, a person usually must inherit two faulty copies of the Niemann-Pick gene, one from each parent. But Ms. Reynolds's disease was unusual, said her neurologist at the N.I.H., Dr. Camilo Toro.

Like children with the disease, she inherited one Neimann-Pick gene that was so mutated it did not function at all. But the other Niemann-Pick gene was normal. Instead, a mutation occurred in a region of DNA that controlled the normal gene, hobbling it.

Unlike most patients, Ms. Reynolds got by for more than four decades before the disease finally started taking a toll.

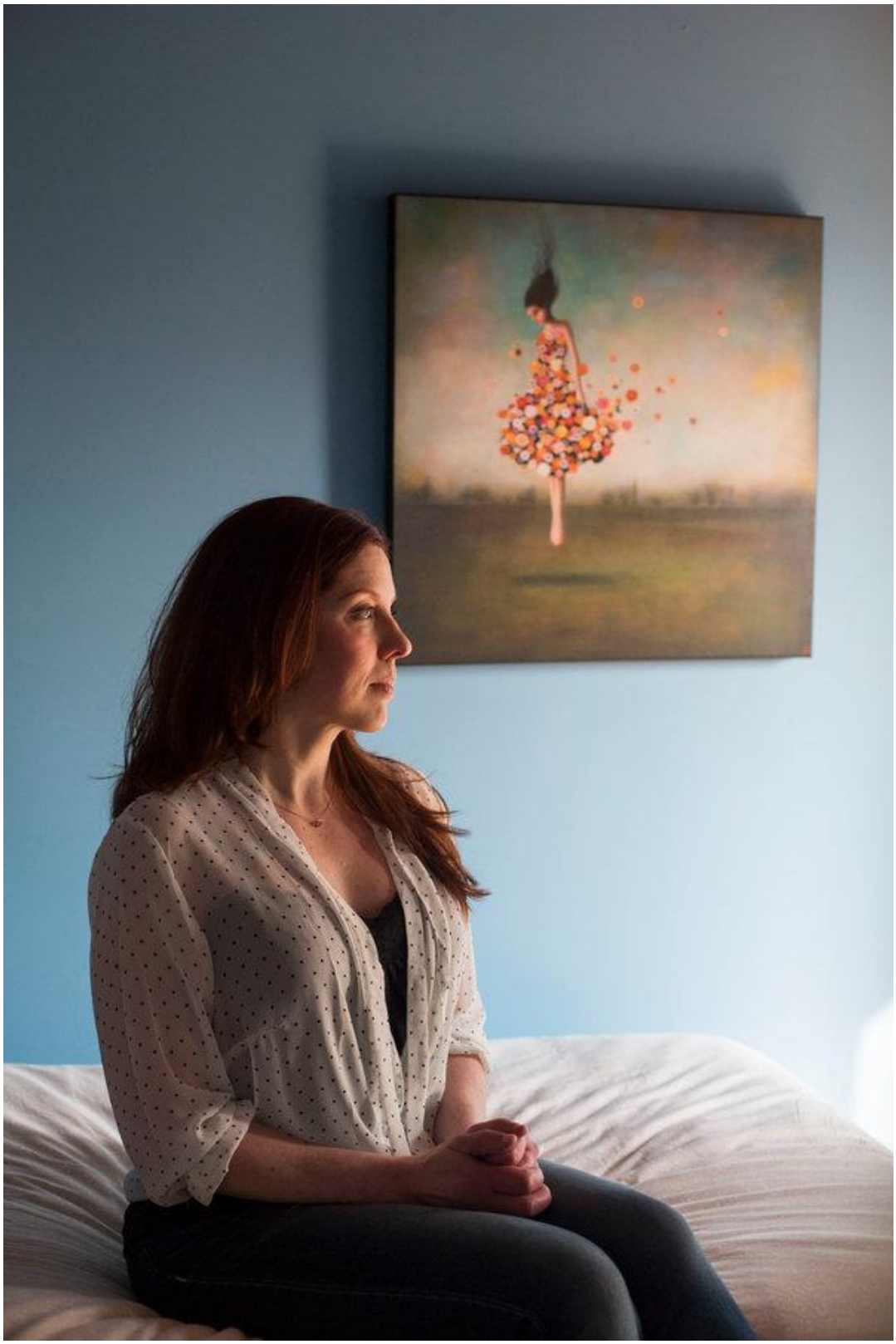
"It is not unheard of to develop Niemann-Pick disease as an adult, but it is very, very rare," Dr. Toro said. "I'd read about it but never seen an adult patient."

The prognosis: It's hard to know. Ms. Reynolds's disease has progressed extremely slowly — but it has intensified. "We could predict worsening of her coordination, gait and articulation," Dr. Toro said. "Late-onset NPC patients often experience neuropsychiatric symptoms, which has not been the case with Ms. Reynolds."

The treatment: There is no approved therapy for the disease. But there are clinical trials of experimental therapies underway. If approved, Dr. Toro hopes Ms. Reynolds may benefit from these treatments.

The diagnosis "helped me deal with the uncertainty," she said. And, she added, maybe one of those experimental drugs will work for her.

She ran marathons until the burning began



Bryan Meltz for The New York Times

Sara Silva, 44. Pacifica, Calif.

The symptoms: Sixteen years ago, Ms. Silva was a healthy marathon runner. Her life changed abruptly, though, after a holiday party for her husband's law firm.

At the event, she suddenly felt a burning, searing pain in her hands and feet. Her legs started swelling. She was frightened, but the next day she seemed fine — so she decided to ignore the episode.

But the symptoms recurred, more and more often until they were with her all the time. The pain and the burning got worse and worse.

"I haven't worn shoes for four years because the pain is so bad," she said. She cannot bear heat: "My house is at 62 degrees, even in winter. I can't cook or use the oven. I can't have warm food or warm showers."

She usually has ice packs on her torso, and she takes heavy doses of pain medications, but not opioids — she is afraid of them.

"This life is challenging," Ms. Silva said. "Pain is something you learn to respect."

Intensive testing: She saw scores of doctors and went to the Mayo Clinic twice for an exhaustive work-up, to no avail. She tried drug after drug to alleviate her symptoms, but nothing helped.

She ended up at the Stanford pain clinic, where doctors said her primary disease is erythromelalgia, a rare condition in which blood vessels become blocked and inflamed. But no one knew how she got it.

Genetic testing yielded no answers. And treatments that help some with the disease did nothing for her. Doctors suspected she might have an underlying medical condition that interfered with drugs to treat the disease.

In early 2018, Ms. Silva was accepted into the Stanford site of the Undiagnosed Diseases Network. She had further genetic testing. As they did for Ms. Reynolds, researchers examined not just her genes, but the DNA between genes that controls them.

Scientists found one stretch of DNA with what looked like an unusual change, but "we didn't have enough evidence to say it was causing her symptoms," said Chloe Reuter, a genetic counselor at the Stanford program.

Ms. Silva's doctors contacted scientists who studied that suspicious genetic region and also looked at healthy people to see if they had a similar genetic change.

The result was a dead end. The scientists found the same genetic alteration in perfectly healthy people. Outside researchers said they really did not think the genetic alteration was causing Ms. Silva's symptoms.

The diagnosis: None as yet. And doctors cannot give her a prognosis. But the Stanford team is continuing to search for answers.

Ms. Silva hasn't given up and said that she is "still hoping to one day get that phone call from them with a solid answer as to what my little monster actually is and how to stomp it out like a hairy spider."

He had meningitis, but there was no infection

Audra Melton for The New York Times

Zarko Stanacev, 67. Atlanta.

The symptoms: In 2007, Mr. Stanacev began having episodes of hearing loss. His hearing came back each time, but then another episode would occur.

His doctor could not figure out what was going on. Then in 2010 Mr. Stanacev was hospitalized with meningitis. He had a high fever and a headache. It was clear that his brain was inflamed, but there was no bacterial or viral infection.

After a few days, he recovered, only to get meningitis again. And again. Between 2010 and 2017, he had 30 episodes for no apparent reason.

The episodes would start with chills and a fever, which would progress hour by hour. “By the next morning he was almost unresponsive,” said his wife, Dejana Stanacev, 55. “Each time he went to the hospital, I didn’t know if he would get out.”

(Because of her husband’s hearing difficulties, Ms. Stanacev told his story on speakerphone with him at her side.)

The disease, whatever it was, kept getting worse. Soon he could not walk and was in constant pain, all over his body. His mind was cloudy; he was unable to concentrate. He spent his time at home "waiting for the days to pass by," Ms. Stanacev said.

Intensive testing: There was no doubt that Mr. Stanacev had meningitis — his brain was inflamed. But why? Antibiotics did not help, and neither did steroids, which should tamp down an inflammation.

No matter how many times he was tested, doctors found no sign of a bacterial or viral infection. Finally, late last year, Mr. Stanacev was referred to the Undiagnosed Diseases Network's site at the N.I.H.

He received the full gamut of testing: imaging, blood draws, genetic analysis and, importantly, a lumbar puncture to obtain cerebrospinal fluid, which bathes the brain. That fluid showed clear signs of extensive inflammation.

At the end of the week, the Stanavecs went home, praying for a diagnosis.

The diagnosis: The Stanavecs got a phone call in April from the clinic. Researchers had figured out what was wrong.

Mr. Stanavec had an extremely rare mutation in a gene, NLRP3, which helps direct cells to activate a protein, interleukin 1 beta, that is part of the immune response to infections. The mutation made him produce an NLRP3 protein that was always active — even when there was no infection.

There are just two or three reported cases of this mutation in the medical literature, said Dr. William Gahl, clinical director of the National Human Genome Research Institute at the N.I.H. It's not clear why Mr. Stanavec's symptoms started so late in life, Dr. Gahl said. Nor is it clear why only his brain was inflamed.

But the good news for him was that there is a drug on the market — anakinra, used to treat rheumatoid arthritis — that blocks interleukin 1.

The treatment: Mr. Stanacev and his wife returned to the N.I.H., and he got an injection of anakinra. His pain melted away. He got up from his wheelchair. He could think clearly again. "It was like a fog lifted from my brain," he said to his wife.

"It was like a miracle," Dr. Gahl said.

Correction: *January 6, 2019*
An earlier version of this article misspelled the surname of a genetic counselor at Stanford University. She is Chloe Reuter, not Chloe Richter.

Correction: *January 7, 2019*

An earlier version of this article misstated the reason that Zarko Stanacev responded to questions only through his wife, Dejana Stanacev. According to her, it was because he has hearing difficulties, not because he is not fluent in English.

Gina Kolata writes about science and medicine. She has twice been a Pulitzer Prize finalist and is the author of six books, including “Mercies in Disguise: A Story of Hope, a Family's Genetic Destiny, and The Science That Saved Them.”