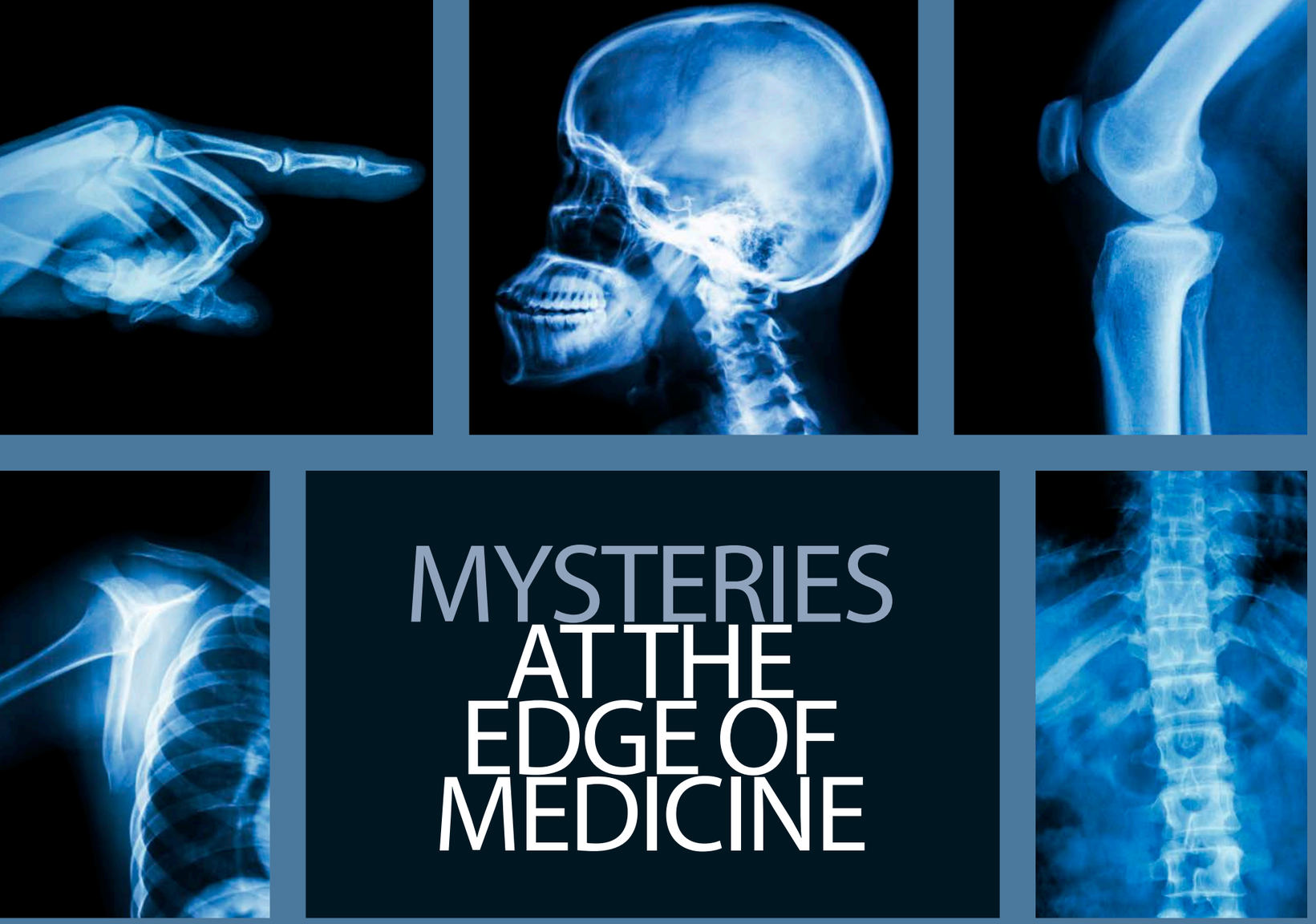


MYSTERIES AT THE EDGE OF MEDICINE

PUWADOL JATURAWUTTHICHAI/SHUTTERSTOCK

MILLIONS OF AMERICANS SUFFER FROM AILMENTS WITHOUT A NAME. THAT'S WHERE THE UNDIAGNOSED DISEASES NETWORK COMES IN.

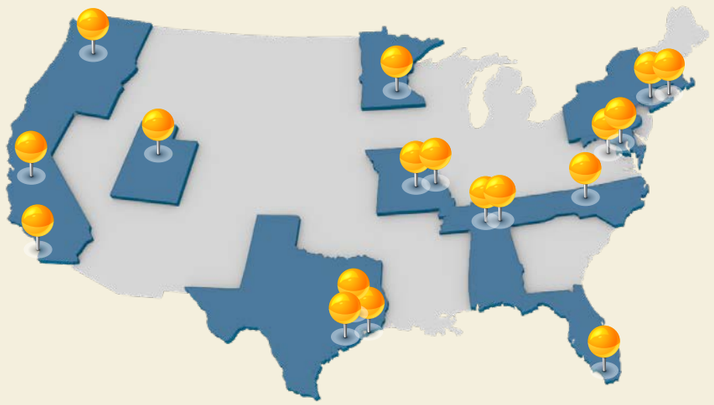
BY NATHANIEL SCHARPING

Elizabeth wouldn't walk or talk as a toddler. Laura's hair fell out, and rashes attacked her skin. Angela's left leg was so swollen it hurt to stand. Emma needed a breathing machine just to sleep. Their suffering may take different forms, but their stories share a common thread: Neither they or their families knew what was actually causing these issues.

Undiagnosed diseases are more common than you might think. Tens of millions of Americans likely suffer from disorders they cannot name. For many, the symptoms are minor. But in some cases, patients come to their doctors with serious problems caused by diseases that defy medical knowledge.

Those cases are precisely where the Undiagnosed Diseases Network (UDN) steps in. Established in 2008 at the National Institutes of Health (NIH), the UDN's mission is to provide answers for patients with diseases that doctors are unable to diagnose. Anyone can apply to the program — with their doctor's blessing — and the UDN endeavors to screen every application it receives.

Today, the UDN encompasses 12 clinical sites around the country, and has evaluated over 1,400 patients, says William Gahl, director of the Undiagnosed Diseases Program in Bethesda, Maryland, one of the network's sites. More than 400 of those patients have received a diagnosis thanks to the UDN and its affiliates. In some of these cases, the network is able to match a patient with an already-known condition. In others, UDN researchers must



SEE THE LOCATIONS →

CLINICAL SITES
- Bethesda, MD (NIH Undiagnosed Diseases Program)
- Boston, MA (UDN Clinical Site at Harvard Medical School)
- Durham, NC (Duke University and Columbia University)
- Houston, TX (Baylor College of Medicine, Texas Children's Hospital, and Baylor CHI St. Luke's Medical Center)
- Los Angeles, CA (UCLA Undiagnosed Diseases Clinic)
- Miami, FL (University of Miami School of Medicine)
- Nashville, TN (Vanderbilt Center for Undiagnosed Diseases)
- Philadelphia, PA (Children's Hospital of Philadelphia and University of Pennsylvania)
- Salt Lake City, UT (University of Utah – Intermountain West)
- Seattle, WA (Pacific Northwest Undiagnosed Diseases Clinical Site at University of Washington and Seattle Children's Hospital)
- Stanford, CA (Center for Undiagnosed Diseases at Stanford)
- St. Louis, MO (Washington University in St. Louis)

CENTRAL BIOREPOSITORY
- Nashville, TN (Vanderbilt University Medical Center)

COORDINATING CENTER
- Boston, MA (Harvard Medical School and University of Alabama at Birmingham)

METABOLOMICS CORE
- Rochester, MN (Mayo Clinic)

MODEL ORGANISM SCREENING CENTERS
- Houston, TX (Baylor College of Medicine and University of Oregon)
- St. Louis, MO (Washington University in St. Louis)

SEQUENCING CORE
- Houston, TX (Baylor College of Medicine)

MEET THE DOCTORS →

From left: Clinical geneticist Dorothy Grange, who works with Laura Ammann; assistant professor of pediatrics Hsiao-Tuan Chao, who helped diagnose Elizabeth Nagorniak; clinical geneticist Carlos Bacino, Emma Broadbent's physician; clinical geneticist Fuki Marie Hisama, one of Angela Moon's lead clinicians.

work to describe an entirely new disease and enter it into the medical lexicon. The program has added at least 25 entirely new diseases in this way, Gahl says. Additionally, the UDN covers the cost of the tests, meaning patients aren't saddled with crushing medical debt.

"It changed everything," says Mari Hanada, whose daughter is a UDN patient. "Suddenly I had a direction; I knew which way to go."

This kind of groundbreaking work helps more than just the patients themselves. Insights from studying rare diseases offer new knowledge about the human body that can benefit all of us. For example, the discovery of statins, a class of drugs commonly prescribed today to help regulate cholesterol, arose from the study of a rare genetic disorder called familiar hypercholesterolemia.

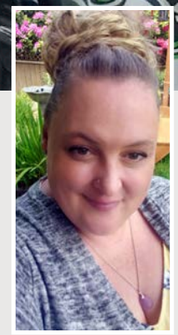
Unraveling these formidable cases requires hours of poring through medical records, batteries of tests, days of examinations and, crucially, close collaboration between specialists in disparate fields.

"I think they've really advanced and changed the whole paradigm [for] how we approach many of these illnesses," says Anne Pariser, director of the Office of Rare Diseases Research at the NIH's National Center for Advancing Translational Sciences. She says the UDN's multidisciplinary approach — bringing different specialists together to talk about challenging cases — has helped advance the field of rare disease research, especially when it comes to genetic diseases.

For many patients, the UDN offers something less tangible, too. Living with a disease without a name can be its own kind of suffering. "You grow up feeling like, 'I'm in this, crazy, all by myself, and no one really understands me,'" says Angela Moon, a UDN participant. For patients like her, the UDN offers hope — for treatment, but also for finally being seen.

MAP: ERNESTO DEL AGUILA III; NATIONAL HUMAN GENOME RESEARCH INSTITUTE. PHOTOS, FROM LEFT: DOROTHY GRANGE; HSIAO-TUAN CHAO; CARLOS BACINO; FUKI MARIE HISAMA

ANGELA MOON / AGE: 46



Top: Angela, along with husband Gordon and daughter Deanna, on a Boston tour bus in 2017. Bottom: Angela in her backyard in 2019.

For decades, Angela Moon dealt with her baffling condition in silence. Some people didn't even realize she had a disability, she says, because she hid it so well. But in reality, Angela was often in pain, the result of thousands of hard, purplish lesions called angiokeratomas that grew on her skin and which could burst open bloodily. Her legs were especially painful, as they were constantly swollen with fluid, a condition known as lymphedema. Though Angela had been evaluated by doctors for her symptoms since birth, there were no real explanations and little respite from the discomfort.

In 2017, everything came to a head. Angela "basically [had] a mental breakdown," she says, the result of years of coping with stress and physical pain, compounded by the absence of any sort of diagnosis. She had to leave her job at FedEx and spiraled into depression. By 2019, she could no longer enjoy even simple activities with her husband Gordon and daughter Deanna.

"I was like, 'I can't do this anymore,'" she says.

It was around this time that Angela began working with the UDN. In January of 2020, she went to the University of Washington Medical Center in Seattle for two days of comprehensive tests, including blood work, MRIs, skin biopsies and more. Though they were grueling, she says the exams felt different than the countless medical appointments that came before — more purposeful and compassionate.

"When you're dealing with a disability, […] you just want someone to understand," Angela says.

It's still too early for the UDN to say what might be causing Angela's symptoms, or whether her disparate symptoms are even related, says Fuki Marie Hisama, a clinical geneticist at the University of Washington School of Medicine and one of Angela's lead clinicians at the UDN. But Angela has already begun laser treatments for the angiokeratomas, something she says has greatly reduced the discomfort and bleeding. And the UDN connected her with a plastic surgeon specializing in lymphedema who has already operated on her left leg, with positive results.

The possibility of further treatment is giving Angela a sense of optimism that's largely been missing for more than four decades of her life, she says. And it's letting her focus on the future, too. An archaeology buff, she imagines one day working at a museum doing project management.

Like others who have worked with the UDN, Angela also anticipates her struggles could help ease the pain of others in the future. Though she once felt embarrassed when doctors brought in medical students to examine her unsolved case, today she's happy to share. "I want to give someone hope," she says. "If they figure out what's going on with me, they can match it with somebody else that comes in in the future."

The possibility of further treatment is giving Angela a sense of optimism that's largely been missing for more than four decades of her life.

GORDON MOON (2)

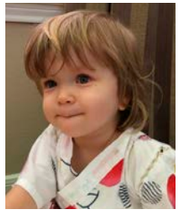
ELIZABETH NAGORNIAK / AGE: 6

In her 26th week of pregnancy, Mari Hanada's doctor ordered a fetal MRI for her unborn daughter to assess what appeared to be irregular brain development. Those scans and some initial genetic tests were initially reassuring. But soon after Elizabeth, now 6, was born, there was new cause for alarm — the infant's head was swollen. At six months, she was diagnosed with hydrocephalus, a buildup of fluid in the brain. Multiple surgeries to drain the fluid followed.

As Elizabeth grew older, more dismaying symptoms began to stack up. She kept missing developmental milestones. She could barely hold up her head, let alone walk. She briefly began to babble at about a year and a half, but soon stopped. "I kept buying toys, trying different things, but she wasn't interested," Mari says. "It was really sad to see her not doing anything."

The family first met with the UDN in 2018, when Elizabeth was 3 years old. Tests up until that point had been inconclusive, and her parents had little idea how to address their daughter's symptoms.

But Elizabeth turned out to be lucky. One of the first things the UDN did, according to Hsiao-Tuan Chao, an investigator with the UDN and assistant professor of pediatrics at Baylor College of Medicine, was examine a unique pattern on Elizabeth's skin. "She was a little bit stripy," Chao says. Light and dark lines alternated across Elizabeth's body; almost tigerlike. It was a hint to Chao that something deeper was amiss. The cells that go on to form both our skin and our brains start from the same population early on. So, when a mutation shows up on the skin, mutations in the brain are expected, too.



Top: Elizabeth, almost 2, tries on her first kimono, sent by her grandmother in Japan. Bottom: Elizabeth, at age 5, sits on a chair at a local park.

The UDN performed more comprehensive genetic tests on Elizabeth's skin. The results revealed a mutation to a key gene known as MTOR that regulates how cells proliferate during development. In Elizabeth's case, the protein produced by the gene wasn't being turned off properly, meaning some groups of cells that should have stopped growing had failed to do so. It explained her stripy skin, but also the developmental delays that kept Elizabeth from progressing.

Fortunately for Elizabeth, MTOR has been researched extensively because it's also involved with tumor growth. That knowledge led doctors to a diagnosis for Elizabeth — and an already-existing treatment.

Elizabeth has a variant of Smith-Kingsmore Syndrome, a rare genetic condition tied to mutations of the MTOR gene. Today, she's receiving a drug called Sirolimus that's led to dramatic changes in her development in just a year. "She's getting new skills weekly now," Mari says. "It used to be annually."

The diagnosis also helped Mari connect to other families with children suffering from the condition. She's since become active in a Facebook group for Smith-Kingsmore Syndrome. In October of 2019, they met with 17 other Smith-Kingsmore families at Cincinnati Children's Hospital. It's marked a turning point in Elizabeth's journey, one Mari never stopped fighting for.

EMMA BROADBENT / AGE: 5

Ever since she was born, Brian Broadbent's daughter Emma has been severely delayed. Now 5, she's at the developmental age of a 5-month-old, he says. Brian and his wife, Julia, must give Emma nearly round-the-clock care to ensure her survival. She cannot feed herself, and may never walk or talk. Emma sleeps with a BiPAP machine — a portable device that pushes oxygen into a patient's airways — to help her breathe. She spent Christmas of 2019 in the hospital on a ventilator.

Shortly after their daughter's birth, the Broadbents embarked on a journey to attempt to understand what their daughter was experiencing. They spent months with a white-matter specialist analyzing Emma's brain and had her genome sequenced. They traveled to the Mayo Clinic for metabolic testing and twice to the Children's Hospital of Pennsylvania for exams. But the results from all that testing weren't very helpful. "She's at the edge of science," Brian remembers one doctor telling them.

In 2017, their search led them to the Rare Genomes Project at the Broad Institute of MIT and Harvard, and the UDN shortly afterwards. Both organizations began sequencing Emma's entire genome, as well as her RNA. And, as it turns out, both groups soon found the same thing: a mutation to the CHD2 gene. Irregularities in this gene are often associated with epilepsy, but Emma's symptoms were far worse.

Uncovering the true root of Emma's symptoms took further digging, and a timely coincidence. It turns out Emma has another mutation on a gene near CHD2 called Chaserr. It's what's known as a long noncoding RNA, or lncRNA gene, and it affects how CHD2 is expressed. Nothing had been known about the gene until just months before, when a team of Israeli researchers published a paper on Chaserr and its role. The paper included data on mice genetically engineered to lack Chaserr, which had brain anomalies similar to Emma's.

In Emma's case, the combination of mutations appears to affect her brain's myelin, the protective sheathing that covers our nerves and brain cells, says Carlos Bacino, a clinical geneticist at the Baylor College of Medicine, a UDN site, and Emma's physician at Texas Children's Hospital. The result is what Bacino describes as a neurodegenerative disorder affecting her brain's development and function. Emma is the first patient in the world to ever be diagnosed with a condition resulting from a lncRNA mutation. There could even be a treatment for her at some point, in the form of a new kind of genetic therapy known as antisense oligonucleotides, which could alleviate some of Emma's symptoms.

Top: Emma (right) relaxes at home with her father, Brian, mother, Julia, and older sister, Claire. Bottom: Emma and Claire play dress-up.

It's bittersweet news for Brian — his daughter is truly at the forefront of modern-day medicine, and that means the chance for a cure is small. But Emma is also offering scientists potentially groundbreaking knowledge. Perhaps the next child born with a lncRNA defect will have the hope of treatment. "She's kind of like a gift to science," Brian says. "It does bring a lot of comfort."

LAURA AMMANN / AGE: 35

Laura Ammann never smiled as a child. She was born with the symptoms of a rare condition known as Moebius Sequence, which restricted her facial and eye muscles from moving properly. The congenital syndrome isn't exactly common, appearing in less than 1 in 50,000 people. But Laura would prove to be a rarer case still: In addition to her facial symptoms, Laura's brain was swollen with fluid at birth, a condition known as hydrocephalus. Further testing revealed that some of her neurons hadn't migrated properly during development.

As Laura grew up, more puzzling symptoms appeared. Her hair fell out in third grade, grew back, and fell out again in eighth grade — this time for good. Skin rashes flared across her body, and her fingernails and toenails wouldn't seal to their cuticles properly, leading to a string of infections. She started having seizures when she was 20.

Left: Laura, at age 7, celebrates Easter with her family. Right: Laura recovers from infusion therapy at SSM Health Cardinal Glennon Children's Hospital in St. Louis in 2019.

"She's really a medical mystery," says Dorothy Grange, a clinical geneticist at the Washington University School of Medicine in Louisville who's worked with Laura for over a decade. "So many complex medical issues and not a single unifying diagnosis." Until 2019, when she began working with the UDN, there was little explanation for Laura's symptoms.

Meanwhile, Laura got on with her life. In addition to a daily exercise routine, she began working at a nearby school for disabled children in 2009, helping students with therapy and schoolwork. Though she has to wear gloves to protect her hands, the work still brings her real satisfaction today. "I hope I have that for the rest of my life," she says, or at least "until they kick me out."

But in 2019, after more than two decades of study by various groups, Grange and researchers with the UDN started to inch closer to an answer to Laura's problems. Grange had already found irregularities in Laura's sterols, a class of lipids, including cholesterol, that play a fundamental role in how our bodies develop and function. Whole-genome sequencing through the UDN turned up a unique variant of a gene related to cholesterol in Laura, providing further evidence for Grange's hypothesis: Her body's deficits in making sterols could be causing her array of seemingly unrelated symptoms.

Researchers with the UDN are currently working with fruit flies genetically engineered to possess Laura's specific genetic variant.

Researchers with the UDN are currently working with fruit flies genetically engineered to possess Laura's specific genetic variant. That work could reveal whether this gene is truly at the root of her problems, and potentially point the way toward her treatment. D

Nathaniel Scharping *is a freelance science writer based in Milwaukee.*

FROM TOP: MARI HANADA; GYULNARA LOKTEVA; ELIZABETH AMMANN (2)

FROM TOP: JAN OSBORN/DALLAS DOING GOOD; JULIA BROADBENT