

# The Genetic Detectives

**A new government program will study, diagnose and ultimately treat people with mysterious diseases.**

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NEWSWEEK

Updated: 1:28 PM ET May 31, 2008

For the first four years of his life, Zachary Townsley was a medical mystery. His mother, Janine, noticed something strange about him at six months: he had "a little hump in his back." The family pediatrician said not to worry, but by one year, Zachary had a new symptom: at an age when most babies were starting to walk, he wasn't crawling. The Townsleys went to a neurologist, but he couldn't find a diagnosis that would explain Zachary's troubles. The results of a chromosomal test came back clean. Occupational therapists, physical therapists, speech therapists, an audiologist: none of them could tell the Townsleys what their son had. By the time he was almost 4, Zachary was walking, but with bent knees. He had developed a speech impediment, and his once angelic facial features had begun to grow in odd proportions. Other kids stared at him on the playground. Clearly, something was wrong. But what on earth was it?

Zachary's story is sadly familiar to millions of Americans who suffer from—well, it's hard to say what they suffer from, and that's the problem. Twenty-five million people are currently afflicted with rare diseases, and for many of them, a proper diagnosis can take years or decades, if it comes at all. Some of these conditions are so new that they don't have names yet. Those that do have names—Blackfan Diamond anemia, periodic paralysis, Hermansky-Pudlak syndrome—may strike just a few hundred or a few thousand people. They can mimic much more common ailments, masquerading as high blood pressure or fatigue. Patients who have them may be misunderstood and misjudged, and they have no choice but to go untreated: doctors throw up their hands in confusion, friends wonder if the symptoms are all in the head. Often, when patients do finally get a correct diagnosis, irreversible damage has already been done. "If they go for 20 years without a diagnosis they can accrue all sorts of complications," says Dr. William Gahl, the clinical director of the National Human Genome Research Institute. "By the time they know what it is they have, they're medical disasters."

Last month it seemed these unfortunate patients might be getting a major new source of help. On May 19, the National Institutes of Health revealed its new Undiagnosed Diseases Program, an interdisciplinary center for studying, diagnosing and ultimately treating patients with unidentified illnesses. In a teleconference, NIH director Elias Zerhouni hailed the initiative's potential, noting that its use of genetics and genomics could be "transforming." Amanda Young, a 26-year-old woman, offered hope, too: she told how she'd waited 20 agonizing years until the NIH's Clinical Center diagnosed her with IRAK-4 deficiency, an extremely rare genetic mutation. Gahl, who heads the new program, also spoke. But his message was more subdued. "This is a research program," he said. "We won't be able to help everyone who seeks our care." Later, in an interview, he worried that his part of the message might have been lost: "A lot of people are going to hear this as 'oh, they have a diagnosis for me!'"

The Undiagnosed Diseases Program may be innovative, but it's also very small. It is equipped to see no more than 100 carefully chosen patients a year, and it consists of just three full-time staffers: two nurse-practitioners and a scheduler, who is suddenly very busy. In the first two weeks of its existence, the program received more than 200 phone calls from desperate patients in and outside the United States. All of them wanted to come to the NIH for full, extensive evaluations. "We're being inundated," Gahl says. The new institute can lean on doctors at other NIH centers for help, but all those docs have day jobs. So, for that matter, does Gahl: he has a lab with multiple ongoing experiments, and the new institute takes up only a third of his time. He hopes the NIH (which is already strapped for cash) will send more funding and employees his way. Until it does, the best the program will be able to do for most patients is guidance by phone call.

Ultimately, what rare-disease patients need is for the program to match or at least approach the success of the Orphan Drug Act, which leverages the enormous resources of Big Pharma for small markets. The legislation is celebrating its 25th anniversary this year, and talk about transformative: it has increased the number of drugs developed for rare-disease markets by about thirteenfold. These drugs are often costly, but they can be the happy endpoint of a rare-disease patient's journey; once a diagnosis is finally given, they allow for something to be done about it. Zachary Townsley, now 8, is one of their beneficiaries. A month shy of his 4th birthday, he was diagnosed with Hunter syndrome, a metabolic disorder that affects only 500 Americans. In October 2006 he began taking Elaprase, a newly approved orphan drug that was—and still is—the only treatment on the market. It is not a cure, but some of his symptoms have improved, and it is far better than the recommendation doctors originally gave Janine Townsley: "Love him, take good care of him, pray and go home."

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