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**HEALTH** | NYT NOW

# In a First, Test of DNA Finds Root of Illness

**By CARL ZIMMER** JUNE 4, 2014

Joshua Osborn, 14, lay in a coma at American Family Children's Hospital in Madison, Wis. For weeks his brain had been swelling with fluid, and a battery of tests had failed to reveal the cause.

The doctors told his parents, Clark and Julie, that they wanted to run one more test with an experimental new technology. Scientists would search Joshua's cerebrospinal fluid for pieces of DNA. Some of them might belong to the pathogen causing his encephalitis.

The Osborns agreed, although they were skeptical that the test would succeed where so many others had failed. But in the first procedure of its kind, researchers at the University of California, San Francisco, managed to pinpoint the cause of Joshua's problem — within 48 hours. He had been infected with an obscure species of bacteria. Once identified, it was eradicated within days.

The case, reported on Wednesday in The New England Journal of Medicine, signals an important advance in the science of diagnosis. For years, scientists have been sequencing DNA to identify pathogens. But until now, the process has been too cumbersome to yield useful information about an individual patient in a life-threatening emergency.

"This is an absolutely great story — it's a tremendous tour de force," said Tom Slezak, the leader of the pathogen informatics team at the Lawrence Livermore National Laboratory, who was not involved in the study.

Mr. Slezak and other experts noted that it would take years of further

research before such a test might become approved for regular use. But it could be immensely useful: Not only might it provide speedy diagnoses to critically ill patients, they said, it could lead to more effective treatments for maladies that can be hard to identify, such as Lyme disease.

Diagnosis is a crucial step in medicine, but it can also be the most difficult. Doctors usually must guess the most likely causes of a medical problem and then order individual tests to see which is the right diagnosis.

The guessing game can waste precious time. The causes of some conditions, like encephalitis, can be so hard to diagnose that doctors often end up with no answer at all.

“About 60 percent of the time, we never make a diagnosis” in encephalitis, said Dr. Michael R. Wilson, a neurologist at the University of California, San Francisco, and an author of the new paper. “It’s frustrating whenever someone is doing poorly, but it’s especially frustrating when we can’t even tell the parents what the hell is going on.”

For the last decade, researchers at the university have been working on methods for identifying pathogens based on their DNA. In 2003 Dr. Joseph DeRisi, a biochemist at the university, gained wide attention for using a gene chip called a microarray to identify the coronavirus causing SARS.

The researchers’ latest method is called unbiased next-generation sequencing. To identify a pathogen, the researchers extract every scrap of DNA in a sample from a patient, which might be blood, cerebrospinal fluid or stool. Then they sift the genetic fragments for those belonging to pathogens.

The technique already has proved valuable for investigating mysterious disease outbreaks, and a number of scientists have begun to hope it can be adapted to the diagnosis of individual patients’ infections. Rather than test for a suspected pathogen, a doctor could simply run a DNA test that could identify the culprit no matter what it is — virus, bacterium, fungus or parasite.

“It could be one test to rule them all,” Dr. DeRisi said in an interview.

But such a test would be useful only if it were fast, and sorting through millions of DNA fragments has been an intensive technological challenge. Playing this match game can take weeks.

"The problem is that your critically ill patient will be dead by the time you make a diagnosis," said Dr. Charles Chiu, a pathologist at the university who collaborates with Dr. DeRisi on diagnostic technologies.

Dr. Chiu and his colleagues have developed software that rapidly compares DNA fragments with genetic sequences stored in online databases. They describe their new strategy in a second paper published on Wednesday in the journal Genome Research.

Last July, Dr. DeRisi and Dr. Chiu got a chance to put their methods to the test when they received a call from a research collaborator, Dr. James Gern, a pediatrician at the University of Wisconsin School of Medicine. He asked them to help figure out what was wrong with Joshua Osborn.

Joshua had long been a patient of Dr. Gern's, since doctors found that the boy had an immune system disorder at two months old. In April 2013, he developed severe headaches and a fever. He was admitted to the hospital and tested for a long list of diseases, from West Nile virus to tuberculosis. The tests all came back negative.

For the next two months, Joshua remained at home, his health wavering. When his fever spiked again, he ended up back in the hospital. An M.R.I. revealed that his brain was dangerously inflamed, but a spinal tap turned up no pathogens. Even a biopsy of his brain tissue told the doctors nothing.

It was then that Dr. Gern called on Dr. DeRisi, who agreed to use the experimental DNA technology to try to find what was causing the boy's ailments.

Dr. Gern's team set about preparing samples of Joshua's cerebrospinal fluid and serum for testing. Dr. DeRisi's team received the samples on Aug. 21, and by that evening, the lab's sequencing machines were working on the first batch of DNA.

Two days later, the machines had deciphered the sequences of three million fragments of DNA present in Joshua's samples. With Dr. Chiu's software, the team set aside the human DNA fragments and began grinding through DNA databases to identify the other genes.

After only 96 minutes, the results appeared on a computer monitor. Joshua's cerebrospinal fluid contained DNA from a potentially lethal type of bacteria called Leptospira. As dangerous as Leptospira can be, it is readily treated with penicillin.

"It was a very exciting phone call to make to Wisconsin," Dr. Wilson said. "Not only was there an answer, but there was something they could potentially do about it."

That afternoon, Joshua started getting large doses of penicillin. The swelling in his brain almost immediately started subsiding, and two weeks after the first test results, Joshua was walking.

"I don't have any headaches anymore," Joshua said in an interview. "It's almost like a rebirth."

Dr. Chiu is now leading a project to develop a DNA-based test for diagnosing the causes of encephalitis and other life-threatening conditions. They also hope to apply it more broadly, as a way to quickly diagnose any infection.

"It's a demonstration that this technology has arrived," Dr. DeRisi said. "It can make a difference in real time."

There are still many obstacles that scientists will have to overcome before these tests can be a part of standard practice.

"Our bodies are full of microbes," said Dr. Gregory Storch, a professor of pediatrics at the Washington University School of Medicine in St. Louis. DNA-based tests will turn up many of those species in any patient sample. Often, it may be hard to figure out which are making someone ill.

"This technology allows us to see the world in a different way, and we have to get used to that," Dr. Storch said.

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