Doctors use sick boy's DNA in diagnosis, treatment

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Doctors and scientists in Wisconsin have published the first detailed account of a groundbreaking medical case in which they sequenced all the genes of a very sick young boy from Monona, Wis., and used the information to treat the child.

Genetic experts said the Wisconsin case signals a new era in medicine in which doctors will be able to read our genetic script to diagnose and sometimes treat maladies, especially cancers and rare hereditary diseases.

The boy, whose story is the subject of a Milwaukee Journal Sentinel series starting Sunday, suffered from a disease and mutation never before seen in medicine. When he ate, painful holes called fistulas would open, leading from his intestine to his skin. The child, now 6, became so sick that doctors had to remove his colon in the spring of 2009.

In a paper published online Friday in the journal *Genetics in Medicine*, doctors and scientists at Children's Hospital of Wisconsin and the Medical College of Wisconsin described how they were able to read the boy's genetic script in the summer of 2009 and pinpoint the mutation responsible for his disease.

"For the patient and his family, it's a benefit and something we all feel really good about," said Howard Jacob, one of the paper's authors and director of the Medical College's Human and Molecular Genetics Center. "It demonstrates that this technology can start being used in the

clinic today."

The case is believed to be one of the first in the world in which the sequencing of a patient's DNA has led to a diagnosis and treatment.

"Everyone's talking the talk about personalized medicine, and this is a real example. We don't have too many of those," said Richard Gibbs, director of the Human Genome Sequencing Center at Baylor College of Medicine.

A team at Yale University accomplished the feat earlier, using a similar technique to diagnose a baby in Turkey born with congenital chloride diarrhea.

The Wisconsin case shows how, with a patient's life at stake, doctors, geneticists and computer experts can work together to make sense out of the vast ocean of information in our 21,000 genes.

"It's a wonderful paper," said Eric D. Green, director of the National Human Genome Research Institute, part of the National Institutes of Health. "It seems like every month now there's a publication like this that demonstrates the power of this technology.

"The novelty of this story is that it was done in real time to help make a decision about clinical management."

As a result of sequencing, the Wisconsin scientists learned that the boy had a defect in his immune system caused by a single mutation in a gene called XIAP. The mutation also caused a second extremely rare disease called XLP, which affects just 400 boys worldwide, rendering them unable to survive Epstein-Barr virus.

Doctors had not previously known that the child had XLP, which can be

treated with a bone marrow transplant. In mid-July the boy received an umbilical cord blood transplant, which is similar to a bone marrow transplant. He was discharged from the hospital in October.

As the doctors point out in their commentary, the new case underscores how the fast-moving revolution in technology is driving breakthroughs in genomics.

"The tools available to make this diagnosis," they write, "were not available when the child first (was hospitalized) four years ago."

Before deciding to sequence his DNA, doctors conducted dozens of tests on individual genes and on his immune system. Yet they were unable to reach a diagnosis.

In Wisconsin, as in the Yale case, scientists decided against sequencing the patient's entire genome, all 3.2 billion chemical base pairs. Instead, they read a little more than 1 percent of the genome, the exons. Exons, part of every gene, carry the instructions for making proteins. The failure to make proteins correctly causes many diseases. The sequencing and analysis of the Wisconsin child's exons cost roughly $75,000 in 2009, though the cost in a couple of years should be $1,000, Jacob said.

Even when doctors decided to sequence all of the boy's genes using this more efficient technique, the task was not simply a matter of waiting for a machine to spit out an answer. Initially, they got a list of 16,124 potential answers - differences between his genetic script and the reference genome that is used as a yardstick of what is "normal."

The Wisconsin researchers developed a software program to help them weed out harmless variations. The child's DNA was run through the sequencing machine five times to reduce the chances of missing a mutation.

Researchers also consulted the medical literature on many genes and the latest database of genetic variations. They were able to drop their list of potential suspects to 32, then to eight and finally to one, XIAP, a gene involved in regulating the immune system. Scientists then ran two tests of the boy's cells in order to confirm that the XIAP mutation caused his illness.

Eric J. Topol, director of the Scripps Translational Science Institute in La Jolla, Calif., called the Wisconsin case "impressive" and said he believes more institutions will use sequencing in the practice of medicine.

"You can just see it taking off," Topol said. "There will be hundreds of these in the next few years, if not much more."