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Genome Cure for Ill Twins Paves Breakthrough to Doctor's Office
2012-01-30 05:01:00.7 GMT

By John Lauerman

Jan. 30 (Bloomberg) -- By the time his twins Noah and Alexis were 12 years old, Joe Beery and his wife Retta had spent a decade trying to figure out what made their children so ill.

After Joe took a job at Life Technologies Corp., a California company that makes DNA sequencers, their luck turned.

The company's machines revealed that the twins had been misdiagnosed and incompletely treated for more than a decade.

New medication put an end to an illness that had caused vomiting, muscle weakness and seizures. Their daughter, who had spells of breathing difficulties that turned her skin blue, was healthy again.

"Genome sequencing literally saved her life," Retta Beery said.

Nine years after scientists sequenced the first complete human genome -- the instruction manual for making all the body's cells -- the industry is poised for a series of takeovers and technological breakthroughs that will bring the technology into doctor's offices and patient hospital rooms. Equipment made by Life Technologies and Illumina Inc. is spewing out human genome sequences faster than ever and prices will soon drop to $1,000, below that of many widely used diagnostic procedures, such as colonoscopies.

Roche Holding AG's hostile $5.7 billion bid for Illumina may spark additional deals as pharmaceutical and diagnostic companies race to bring DNA scanning into routine medical use, analysts said.

## Changes in Oncology

The explosion of genomic data is creating a revolution in the treatment of some genetically driven diseases, especially cancer, said Harold Varmus, director of the U.S. National Cancer Institute. With an exact understanding of the genetic alterations causing individual tumors to grow uncontrollably, doctors can target therapies for better effectiveness, he said.

"It's the biggest change I've ever seen in oncology," he said in an interview. "People are taking genetic information they see in patients' tumors and changing therapy in dramatic ways."

The surge in clinical use of genomics will increase the global market for sequencing products to about $10 billion from the current $1.5 billion over the "next few years," according to Life Technologies Chief Executive Officer Greg Lucier. That would exceed the $3.8 billion global market for magnetic resonance imaging machines. Ross Muken, an analyst with Deutsche Bank AG in New York, said it may take 15 years for the sequencing market to reach Lucier's estimate.

## Inaccessible to Most

Huge obstacles loom. While the Beerys benefited from Joe's job at Carlsbad, California-based Life Technologies, whole genome sequencing isn't routinely covered by insurers. The procedure currently remains inaccessible to most patients unless they have the persistence to be chosen for clinical research studies, or can pay out of pocket.

Just as important, the volume of data that needs to be organized and analyzed is smothering efforts to make the genome applicable to day-to-day medicine. Each person's DNA code contains 6 billion chemical letters, called bases, and differs from what's considered "normal" at more than 3

million of those points. Doctors are still learning the medical significance of the millions of variations. Most of the gigabytes of genetic data churned out by sequencers around the world is, for now, incomprehensible to scientists, let alone people who see patients daily.

## 'Tidal Wave'

"We are standing on the beach, and a tidal wave of information is coming toward us," says David King, CEO of Laboratory Corp. of America Holdings in Burlington, North Carolina, which does medical testing.

Health insurers are also reluctant to underwrite testing such as a full genome sequence that may encourage plan participants to use and demand services that might be needless in many cases, King said at a conference at Harvard Medical School in Boston last year.

"If you want to see their hair stand on end, ask them about a test that's going to be offered to everyone to see if they have some genetic predisposition to obesity or diabetes or something else," King said. "They will run from the room screaming."

Even if it costs just $1,000 to sequence a genome, there are questions that must be answered before insurers will pay for it, said Susan Pisano, a spokeswoman for America's Health Insurance Plans, a Washington-based industry group.

"It's whether there's evidence that it makes a difference to the health of individuals," Pisano said. "Are we confident that there's an adequate level of accuracy? And what are we going to do with the results?"

(Bloomberg News is examining the personal, medical and business impact of genome sequencing. Reporter John Lauerman gave a blood sample in September for sequencing, and the results will be detailed in a future article.)

## How It's Done

Most sequencers are high-powered cameras costing from $50,000 to $700,000 that can read and arrange the four chemical bases of DNA -- called A, C, G and T -- quickly, accurately and in order. DNA from a person's tissue is chopped into pieces, assembled on a slide, and the four bases are labeled fluorescently or with some other marker, so they can be detected by a camera. Finally those millions of pieces are reassembled into one single DNA sequence.

Machines with newer technology, such as Life Technologies' Personal Genome Machine and Ion Proton sequencers, sense the different chemical bases by measuring the release of hydrogen ions from each "letter" of the DNA alphabet. QuantuMDx, a closely held U.K. company, has designed a mini-sequencer the size of an iPod that could be used to test patients for infections and drug responses.

Sequencing efficiency is racing ahead. Clifford Reid, CEO of Complete Genomics Inc. in Mountain View, California, said his capacity will multiply by thousands of times in the next two to three years.

## Venture Backing

The next challenge is developing software and gadgets to help put sequencing information to use in hospitals and physician offices. Google Inc.'s Google Ventures fund, which invests as much as $200 million annually in startups, has put a "significant" chunk of its money into companies aiming to speed the use of the genome, said Krishna Yeshwant one of its partners.

Closely held companies such as GenomeQuest, based in Westborough, Massachusetts, Emeryville, California-based Omicia Inc. and Softgenetics LLC in State College, Pennsylvania, are making software to search through gene variations and find those that are "actionable," for doctors trying to diagnose and treat disease. Knome Inc., co-founded by Harvard Medical School geneticist

George Church to sequence genomes for the public, has reorganized as a DNA analytics company, and will begin licensing software to hospitals and clinics this year, said Jason Lee, chief marketing officer.

## Months to Minutes

Martin Reese, CEO of Omicia, hired a software developer with experience both at Apple Inc. and Wal-Mart Stores Inc. to develop a system that would sort huge numbers of genetic variations, select those that were most likely to be associated with disease, and make it easy for users to process the results.

"We're taking a process, hand annotation of the genome, that can take up to six months to do, and automating it so that it takes just a half hour or an hour," Reese said.

Like the computer industry 20 years ago, gene-sequencing companies are also aiming to make smaller, friendlier products.

During an interview in his office, Jay Flatley, the CEO of San Diego-based Illumina, waved an Apple iPad loaded with an app that displayed his genome. He skipped from page to page with his fingertips. Patients could take this information with them to a doctor's appointment, he said, and discuss treatments.

## Hospital Investment

"What people want to know is, what genetic variants do I have that are different for a disease or drug?" he says, quickly paging through screens of diagrams, text and color icons. He stopped on one describing a gene that would affect his response to the blood-thinner warfarin, should he ever take it.

"I'm in the high-sensitivity category, so I should get a lower dose."

Roche said Jan. 25 that it had offered $5.7 billion, or $44.50 a share, for Illumina. The sequencer manufacturer countered with a so-called "poison pill" measure that would give shareholders the option of buying preferred stock to match each of their common shares, which may make the company too expensive for Roche to buy.

The power of sequencing is spurring hospitals and clinics to invest. Dana-Farber Cancer Institute in Boston plans to buy at least two sequencers from Illumina this year, said Barrett Rollins, chief scientific officer of the Harvard-affiliated oncology center. Doctors at the University of Iowa use GenomeQuest's software to sift through deaf children's DNA to determine whether they're likely to benefit from hearing aids or cochlear implants.

## Misdiagnosed Children

The Beerys' introduction to sequencing began at a 2008 job interview. Joe, 49, was chief information officer at US Airways Group Inc. and Greg Lucier, chief executive of Invitrogen -- which later became Life Technologies -- was trying to recruit him.

At a dinner overlooking the Pacific shore in Del Mar, California, the Beerys described to Lucier and his wife how their children had been misdiagnosed with cerebral palsy at the age of 2. Alexis had muscle weakness and general fatigue that worsened each day from the morning on.

"We went through so many invasive tests through the years," Retta said. "Between the two of them, I'm sure it's been more than a million dollars from insurance and what we've paid."

## Good Night's Sleep

Retta described scouring the literature for conditions that fit the strange symptoms. When the twins were 5 1/2 years old, she read about a rare disorder called a “dystonia,” caused by a deficiency of a nervous system chemical. It sounded similar to what the children were suffering from and was caused by a shortage of dopamine, a nervous system messenger molecule.
Doctors treated the condition with a dose of a drug called Sinemet.

“Alexis took a quarter of a pill, and she slept through the night for the first time in her life,” Retta said.

Lucier told the Beerys that Invitrogen was about to purchase a sequencing company called Applied Biosystems, a move that would later result in the company being renamed Life Technologies. Applied’s sequencers had the potential to find faulty genes in children in just weeks or months, rather than the years-long odyssey the Beery twins, then in their early teens, had endured, Lucier said.

“When you help me merge these companies, there’s a possibility we’ll have the technology to sequence kids with problems like these at birth,” Joe Beery recalled Lucier saying.

“On the way home, I already knew that this was a company that I wanted to be a part of,” said Joe, who signed with Life Technologies within about eight weeks.

## Symptoms Reappeared

A few months after that, the Beery twins’ treatment started to lose effectiveness, and some of the children’s symptoms reappeared. Alexis’s were particularly frightening and severe.
During a two-month period, she went to the emergency room seven times because she was turning blue from lack of oxygen, Retta recalled.

In 2009, Joe and Retta were listening to a presentation by Eric Topol, a Scripps Research Institute scientist who has organized several large genetic studies. As Topol talked about the power of sequencing to solve medical mysteries, a thought began to take shape in Retta’s mind: why not sequence the children’s genomes?

## DNA Decoded

Through Life Technologies’ sequencing division, Joe and Retta got in touch with a team of doctors and scientists at Baylor College of Medicine’s Human Genome Sequencing Center in Houston. One of the Baylor researchers, James Lupski, had sequenced his own genome to identify the mutation behind his case of an inherited nerve disorder, called Charcot-Marie-Tooth disease.

The Beery children’s DNA was decoded in two months by Baylor’s Richard Gibbs on Life Technologies’ machines, the sequencers the Beerys learned about in the dinner at Del Mar.
Life helped pay for the procedure, along with Baylor research funds. Baylor’s doctors and scientists then performed the analysis. As the process went forward, Joe would take a few minutes during his regular work meetings with Lucier to update him on progress.

“I wanted to stay close to it,” recalled Lucier, who later had his own genome sequenced. “It was one of the first full human genome sequencing efforts to study a disease, and I wanted to make sure it did not disappoint.”

## Alive and Healthy

The procedure revealed that the twins had been incompletely diagnosed. In addition to the dopamine deficiency, the dystonia was being caused by a second genetic mutation that interfered with a separate nervous system chemical, called serotonin. The twins’ doctors found that the dystonia could be fully treated with a serotonin replacement that was readily available through pharmacies. The change was dramatic: soon Alexis was back to school, track and basketball. A small dose also helped Noah, who had been less severely affected by the deficiency.

News spread quickly through Life Technologies' offices that the sequencing had helped save the Beery twins. Last summer, Joe told the story to a crowd of hundreds of Life Technologies employees, with the twins present. He explained how he saw the work of the company's employees playing a key role in keeping his children alive and healthy.

"People were crying," Lucier recalled. "People came up to the Beerys afterwards to hug them and thank them for their courage in doing this. It allowed all our employees to draw a line between their work and making life better for patients."

## 'Prayers Answered'

Earlier this month, the company introduced the Ion Proton sequencer, a $150,000 machine Lucier says will be able to sequence an entire human genome in one day for a cost of about $1,000. Until now, most sequencers have been sold to the research community. While that's an important market, the potential for sales to hospitals, clinics and testing laboratories is far larger, Lucier said.

The Beerys said they hope more parents and children will be helped as they have been. Joe Beery said that while he and his family always prayed for guidance, they never dreamed that the answer to their children's health mystery would arrive because he landed at a company that took a gamble on genome sequencing.

"The fact that I ended up where I ended up, you have to believe those prayers were answered," he said.

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