New technology maps human genome in days

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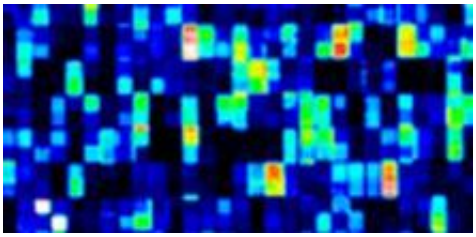

The two 3-by-1-inch glass chips held the unfathomable amount of genetic information contained in 16 human genomes. Last week, a technician placed the chips - called flow cells - in a new genetic sequencing machine at the Genome Institute at Washington University and closed the door.

In just three days, the task will be complete.

It's mind-boggling given that it took scientists working all over the world more than 10 years and about $1 billion to first sequence the human genome, a feat declared officially complete in 2003.

This ultra-fast sequencing machine, which hit the market last year, is only sold in groups of 10 - a system capable of sequencing 18,000 human genomes a year at just $1,000 to $1,500 per genome.

Washington University's Genome Institute is receiving its 10th HiSeq X

machine, each one costing $1 million.

The massive increase in speed and drop in the cost of sequencing allows scientists to take on studies of unprecedented scale, which is necessary to make the conclusions and discoveries about human disease that doctors can put into everyday practice with personalized treatments.

"We have an opportunity to push genomics into the clinic and understand what causes disease and ultimately learn how to predict disease," said Rick Wilson, director of the Genome Institute.

That was the goal and hope when laboratories like the Genome Institute joined together in the early '90s to tackle the seemingly impossible task of mapping the human genome.

"It's like being right at the beginning," Wilson said. "It's like a rocket ship, really. This rocket ship will take us places the old rocket ship couldn't."

When the technology was first announced last year, quantitative biologist Michael Schatz of Cold Spring Harbor Laboratory in New York likened it to the development of the telescope or the microprocessor, which made the modern personal computer possible.

Schatz told the scientific journal *Nature*, "If there was any doubt that genomics would ever be able to reach the everyday man, at this price point and efficiencies, it is absolute certainty."

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What in our genes causes us to have arthritis, diabetes or a cancer that doesn't respond to treatment? To uncover the answers in the 6 billion bases of DNA that make up the human genome requires sequencing

populations.

"If you have 10,000 people with Alzheimer's and 10,000 people who never, never showed signs of the disease, the idea is that you could sequence both those groups and learn something about Alzheimer's," Wilson explained. "Because every human is different from every other human, you can't do that with just five people with Alzheimer's and five people without. You won't have enough data to pinpoint the differences."

That is the reason the new sequencers are sold in groups of 10, according to their maker, San Diego-based Illumina.

"These systems support large-scale human whole genome sequencing projects," said Illumina senior project manager Joel Fellis. "The goal is to deliver both a compelling price and the sequencing capacity needed to sequence thousands to tens of thousands of samples."

The $10 million price also ensures that only institutions equipped with the expertise to decipher and store the data are sitting at the high-stakes poker table of genomics. The Genome Institute is one of seven laboratories in the U.S. that have the HiSeq X Ten and one of 20 worldwide.

"I felt that if we didn't buy into the state of the art technology, there was a possibility we would be left behind," Wilson said. "I thought it was important to the region to continue to have one of the best places in the world to study modern genomics."

The Genome Institute was a key player in the Human Genome Project, ultimately contributing 25 percent of the blueprint, thanks partly to quadrupling the speed of sequencing by developing a way to identify the four bases that make up DNA with fluorescent dye and lasers. In 2008,

the institute was the first to sequence the cancer genome of a leukemia patient and has since sequenced 750 pediatric cancer patients, leading to discoveries in 22 types of cancer.

"The Genome Institute has been a pioneer of both Illumina technology and human whole genome sequencing, particularly in the study of cancer genomics," Fellis said. "Many of the world's first cancer genomes were sequenced in St. Louis, and we are excited to see how they use this technology on a massive scale."

While the institute has learned a lot by sequencing a person's cancer cells and normal cells and comparing the two, Wilson said he is seeking federal grants to use the new sequencing technology to uncover genetic clues about more complex diseases such as heart disease, diabetes and auto-immune disorders.

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Twenty-five years ago, scientists dispensed solutions into a large test tube where they prepared DNA to be sequenced. The process evolved from smaller test tubes to a tray of 96 centimeter-size wells filled by robots. The number of wells further increased to 384. Next came millions of tiny divots on a plate.

The flow cell contains a lawnlike surface that can hold about 3 billion DNA molecules that can all be sequenced at the same time - which scientists call "massively parallel."

"The chip is like thousands and thousands of lab technicians sitting at a lab bench," Wilson said. "There's a whole bunch of stuff happening at the same time."

Rooms of equipment and lab technicians at the Genome Institute have

been replaced by rooms of researchers sitting at computers. Bob Fulton, director of project management, said he never imagined he would be spending much of his day in front of a screen, looking at machine matrix data and quality measurements.

"I don't even know where my lab coat is," he said, laughing. "Tours of this place used to be so cool with robots moving and lifting and squirting things. Now it's boring. It's nothing flashy."

The massive breakthroughs on the sequencing side have required equal advancements in the ability to store and analyze the information output. One human genome alone contains enough data to fill a phone book the size of the Washington Monument.

Across the street from the Genome Institute is a 12,000-square-foot data center housing super computers and servers with its own cooling plant and electrical substations. The equipment is constantly being upgraded with the latest technology, Wilson said, and software engineers are always working to develop new ways to compress the data, make faster comparisons and quickly delete what is not needed.

Given the break-neck speed of advancements in genomics over the past 20 years, the trajectory is hard to imagine.

"In five years," Wilson said, "my iPhone or something like it is going to sequence my genome."