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Innovations

Next Generation Technology Edges Genome Sequencing toward the Clinic

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In the coming years, a copy of your personally sequenced genome could become part of your medical record. As high-quality sequencing information is becoming increasingly available at lower costs and at a faster pace than was possible even a few years ago, geneticists are talking about the possibility of whole-genome sequencing becoming the standard of care in medicine.

Researchers use whole-genome sequencing to find associations between single nucleotide polymorphisms, or SNPs, and disease risk. These changes in the genome account for most of what makes humans differ from one another and could, for example, help explain why certain chemotherapy works in some people but not others or why some people are at a higher risk for certain diseases like diabetes. However, technology seems to be racing ahead of the ability to cope with so much sequencing information. Experts say that many issues need to be resolved, such as how sequences acquired for clinical purposes should be collected and stored; how patient privacy will be addressed; how, when, and by whom, the information will be accessed; and how the general public and the medical community become educated enough to used and understand sequencing information.

There have already been a few instances in which whole-genome sequencing has been used in ways meaningful enough to diagnose, manage, and treat a complex disease. Earlier this year, the team at the Genome Institute at Washington University in St. Louis, Missouri, used information gleaned from whole-genome sequencing to diagnose and treat a woman with leukemia (Link et al., 2011). At a cost of around $40,000, the team sequenced the whole genome of a woman at the request of her doctor. Her cancer had features of two types of leukemia, each of which would require different treatment. The woman's genome was sequenced and analyzed in seven weeks, which was enough time to determine that she did not need a bone marrow transplant. Timothy Ley, M.D., a professor of medicine at the university who cares for leukemia patients, says he plans to use the same type of sequencing to help clearly determine which patients with acute myeloid leukemia (AML), a cancer of a certain type of white blood cell, need a bone marrow transplant. In about half of people with AML, such a determination is difficult. He is currently working to obtain funding for that effort.

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Geneticists are preparing for the day when healthy patients, perhaps starting at birth, have their genome sequenced as part of routine care. At the joint meeting of the International Congress of Human Genetics and the American Society of Human Genetics (ICHG/ASHG) held last October in Montreal, participants in several sessions discussed the advantages and disadvantages of such a change in clinical care, as well as the technological advances that will make this effort possible. In one session, industry leaders presented current and future clinical applications of next-generation technologies. In a plenary debate, industry and academic leaders discussed how next-generation sequencing could change medical genetics and debated how quickly such technology should be used as standard medical care.

Next Generation Sequencing

In an ICHG/ASGH media panel titled "The Future of Next-Generation Genomics Tools in the Clinic," participants discussed the cost of whole-genome sequencing and also talked about steps necessary to make the data relevant and accessible to physicians. There's been much talk of the $1000 genome, but costs will likely drop lower than that.

Roopom Banerjee, president and CEO of RainDance Technologies (http://www.raindancetech.com/), based in Lexington, Massachusetts, calls the $1000 dollar genome "so 2009," but adds that $1000 dollars is still too high for the private pay market and wondering whether a high-quality sequence could be obtained for that amount. He says he wants to see whole-genome sequencing costs come down to several hundred dollars. In the meantime, improving the ability to interpret the information would be useful.

The traffic jam slowing data is partly caused by falling sequencing costs and high-quality data, says Martin Reese, Ph.D., cofounder and CEO of Omica (http://www.omicia.com/). An infrastructure that includes software engineering, informatics, and interpretation at a speed that is clinically relevant will allow physicians to focus on the clinical aspects of sequencing information.

A near-term clinical application of the third generation sequencing technology is underway at Pacific Biosciences in Menlo Park, California (http://www.pacificbiosciences.com/). One effort by the company is applying targeted genome sequencing (choosing a specific part of the genome on which to focus a search) for the metabolic screening of newborns, a program the company announced recently would start at Mount Sinai Medical Center in New York.

Eric Schadt, Ph.D., CSO at Pacific Biosciences and director of the Institute for Genomics and Multiscale Biology at Mount Sinai, says the technology can also be used to turn infection samples around quickly in hospitals by monitoring the surfaces in intensive care units and

for hospital acquired infections and sequencing the samples in the same day.

Schadt says at the end of the day, information from whole-genome sequencing will have to be integrated with metabolites, proteins, and RNA. "We view DNA as a series of letters, but that is wrong. There are chemical modifications to these bases that can alter their chemical composition and change how genes act…understanding these interactions is critical to understanding the genome. We're just scratching the surface of what needs to be detectable from the third generation sequencing technologies," says Schadt.

Brakes or Accelerator on the Translational Highway?

The impact that an abundance of sequencing information will have on the healthcare community and on society goes beyond what technological advances are capable of accomplishing. At the plenary debate session, "Current and Emerging Sequencing Technologies: Changing the Practice of Medical Genetics," experts in the public and private sector tackled the societal issues of using whole-genome sequencing in the clinic. Although doctors other than medical geneticists can order genetic tests, primary care physicians may not be able to interpret the sequencing results or understand that variations in the genome (or SNPs) may not always be linked to a particular disease risk.

The debate centered on the ethical and societal issues that need to be addressed, such as the fact that genetic counselors are already in short supply and that insurers may not want to reimburse for testing. Some panelists expressed concern that the public and even the health care community are not educated well enough in genetics. Others worried that that geneticists could be over promising the ability of whole-genome sequencing because the "translation highway" doesn't just go from the patient to the technology to the doctor and then back to the patient, but that the implications of using whole-genome sequencing in medical care represent a complex issue that reaches into all of society.

Louanne Hudgins, M.D., FACMG, a practicing clinical geneticist at Stanford University in Palo Alto, CA, says that the need for a better public understanding of genetics reaches into the medical community, as well. It's easy for doctors other than geneticists to order genetic tests but that "primary care physicians are ill prepared to interpret sequencing results. I get calls from doctors who don't understand the difference between genes and chromosomes," says Hudgins. Furthermore, Hudgins says that insurance providers may not want to cover the cost of whole genome sequencing.

On the technical side, interpreting the three to four million variants found in genomes, along with nonsense mutations, also needs to be addressed.

Not everyone on the panel urged caution. Radoje Drmanac, Ph.D., CSO and cofounder of Complete Genomics, a whole-genome sequencing company in Mountain View, California (http://www.completegenomics.com), calls for whole-genome sequencing for everyone, starting at birth. "We should celebrate our new ability to sequence complete personal genomes because we didn't have that a few years ago," he says. Drmanac adds that Complete Genomics is on track to sequence over 3,000 personal genomes by the end of 2011. Because next-generation sequencing technology is scalable, the next three or four years should bring the ability to sequence one million genomes per year at an affordable cost says same Drmanac. That number is necessary to make whole-genome sequencing clinically relevant because the database of personal genomes needs to reflect the ethnic diversity of the world population, and there are millions of newborns per year.

He advocates for obtaining whole-genome sequencing as early as possible, on newborns and even as early as in vitro fertilization, when applicable. Whole genomes are needed, continues Drmanac, because genes and genome regulatory networks are so intertwined that all of the information is necessary to help provide the context necessary to interpret biology of cells and organism.

"There's no deeper genetic level than the complete genome sequence," says Drmanac.

REFERENCE

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