Integrating Genomic Sequencing Into Clinical Care

Six studies are underway to determine the medical, ethical, and financial feasibility of the routine mapping of patients' genes.

By Jo Cavallo
September 1, 2013
Tweet this page

Although the price of next-generation genomic sequencing is coming way down, making it available to more people interested in determining their risk for disease, figuring out how to interpret the results and applying that information in the routine medical care of individual patients remains a complex issue, especially for diseases like cancer. What diseases or individual susceptibilities will be most usefully addressed by genomic sequencing and how physicians—many of whom are unfamiliar with interpreting large-scale genomic data—can incorporate that data into real-world clinical applications is the subject of the Clinical Sequencing Exploratory Research (CSER) program, which was launched by the National Human Genome Research Institute in 2011.

The program is designed to study the methods needed to integrate whole-genome and whole-exome sequencing into the clinical care setting and explore the ethical and psychosocial issues raised by applying personal genomic data to medical care, including the implications of reporting unintended findings. The program will also seek to identify best practices and develop methods on how best to disseminate the information to physicians and patients.

To accomplish these goals, last year, CSER began awarding multimillion-dollar 4-year grants to a consortium of clinicians, researchers, bioinformaticians, and ethicists at six institutions. The academic centers and their areas of investigation include Baylor College of Medicine, Houston (Incorporation of Genomic Sequencing Into Pediatric Cancer Care); Brigham and Women's Hospital, Boston (Integration of Whole Genome Sequencing Into Clinical Medicine); Children's Hospital of Philadelphia (Applying Genomic Sequencing in Pediatrics); Dana-Farber Cancer Institute, Boston (The Use of Whole-Exome Sequencing to Guide the Care of Cancer Patients); University of North Carolina, Chapel Hill (NC GENES [ncgenes.org], which is establishing best practices to guide implementation of genomic technologies to improve human health); and the University of Washington, Seattle (Clinical Sequencing in Cancer: Clinical, Ethical, and Technological Studies).

These clinical sequencing projects will be divided into three areas: integrating genomic sequencing into patient care, sequencing and analyzing the data, and studying the experiences of physicians and patients.

Determining the Right Amount of Knowledge

"Before DNA sequencing becomes widely accessible to physicians or directly to patients through commercial laboratories, we are interested in learning what we find when looking at the genome of a generally healthy adult or an adult with a specific disease—in our case, cardiomyopathy—and ask the question, how will physicians and patients understand and use this type of information in health care?" said **Denise M. Lautenbach, MS**, Genetic Counselor and Project Manager of MedSeq Project, Brigham and Women's Hospital and Harvard Medical School, Division of Genetics, in Boston, and a member of the team studying integration

of whole-genome sequencing into clinical medicine. "Our challenge is to set up a process to orient and train physicians in this sequencing technology, which they didn't learn in medical school, and give them the tools and resources to navigate this information with their patients."

The study at Dana-Farber Cancer Institute is investigating the creation of a workable model for the integration of clinical sequencing into cancer care, as well as examining patient preferences for the type of data they want to receive. The study researchers are in the process of sequencing the whole exomes of 400 patients with solid tumor cancers, primarily lung and colon cancer, to determine, in part, the usefulness of generating whole-exome level sequencing data. (In contrast, several academic cancer centers are sequencing just targeted mutation or gene panels.) Enrollment began earlier this year and currently there are nearly 50 patients in the study.

The Broad Institute of MIT and Harvard will do the exome sequencing and both Broad and Dana-Farber will review the data. The patients are asked at the time of consent about whether they want to receive incidental results—for example, information about a gene that predicts an increased risk for Alzheimer's disease—and the experiences of those patients who opted in to receive the information will be assessed. Patients will also be given the opportunity to have genetic counseling at any point during the study. About 27 oncologists will also be surveyed about their experiences receiving and using the data.

"In addition to wanting to know how useful data from whole-exome sequencing is to clinicians, we also want to know if the information transforms their ability to guide clinical trial enrollment. We're trying to understand if having all this information is a good or a bad thing or somewhere in-between," said **Levi Garraway, MD, PhD**, Associate Professor of Medicine, Harvard Medical School and Dana-Farber Cancer Institute and co–lead investigator of the whole-exome sequencing study.

Dividing Mutations Into Actionable Strategies

To help answer that question, Dr. Garraway's group is developing a strategy to place sequencing data into two-tier mutation categories. "The top tier of information would include actionable mutations like *EGFR* with *MET* amplification. The second tier would also include information that is potentially actionable based on literature showing these genes are linked to druggable pathways," said Dr. Garraway.

"Some oncologists may look at the top tier and say 'If I don't see anything interesting in the data, I'm not going to use the information.' Others might say, 'I've run out of options for my patient so I'm going to dig deeper into the data because it may help me find a clinical trial that I wouldn't have thought of before,'" he said.

The study will also evaluate the psychological impact on patients of having this level of genomic detail. "We presume that having genetic information is a good thing, but it may not be. Or if the information is presented and reported in the wrong way, it may end up being confusing and overwhelming and cause patients more anxiety rather than be empowering for them," said Dr. Garraway.

Factoring in Cost

In addition to learning about the medical impact—and benefit—of whole-genome and whole-exome sequencing, the CSER projects are also investigating the economic impact of the ubiquitous use of this type of screening on a health-care system already buckling under the weight of soaring costs.

"Even as the cost of whole-genome sequencing comes down, there is still the cost of manpower to interpret, report, and update the results," said Ms. Lautenbach. "One of the big questions in the field of genetics is about whether we are going to provide too much information to our physicians or information that is so uncertain it necessitates additional tests to follow-up on the results to rule out a diagnosis or to look into something just to be safe, and spend a lot of money in the process. No one knows the answer to that."

Conversely, widespread use of genomic sequencing will also enable oncologists to personalize treatment, reducing both the use of high-cost drugs that are ineffective against the cancer cell's molecular pathway and potentially serious side effects warranting additional treatment.

It could also change the way clinical trials are designed, streamlining a cumbersome process, and limiting a drug's failure rate, perhaps reducing the cost of a clinical trial.

"We appreciate that cancer has to be thought of as many, many rare diseases, and that means that you can't think of cancer the same way you thought of it in the old days when you had a phase III trial of 1,000 patients with lung cancer. Now we have to think about how to become nimble and use sequencing to recognize that,

for example, a given tumor isn't simply 'lung adenocarcinoma.' Perhaps it is lung adeonocarcinoma that has a *KRAS* mutation, *STK11* mutation, or other relevant genetic changes, and we must use that information to target treatment," said Dr. Garraway.

Although the CSER studies are scheduled to end in 4 years, some of the findings will be published in medical journals ahead of that date. ▪

Disclosure: Ms. Lautenbach reported no potential conflicts of interest. Dr. Garraway is a founder, consultant, and equity holder in Foundation Medicine, a company building a genomic-based diagnostic product.