BWH to Use NHGRI Clinical Sequencing Grant to Study Implementation of WGS-Informed Medical Care

January 04, 2012

By Molika Ashford

Starting later this year, Brigham and Women's Hospital will begin enrolling subjects in a National Institutes of Health-funded clinical trial examining the use of whole-genome sequencing in medical care.

In December, the BWH effort, called MedSeq, received a four-year, $9.6 million grant from the National Human Genome Research Institute under its new Clinical Sequencing Exploratory Research Project program to fund the design and implementation of the trial. Four other centers — the Children's Hospital of Philadelphia, Baylor College of Medicine, the University of North Carolina Chapel Hill, and the University of Washington — also received funding under the NHGRI program (*CSN 12/6/2011*).

The goal of MedSeq is to compare medical care informed by whole-genome sequencing against standard care without whole-genome sequencing. The study will follow 200 doctor/patient pairs — 100 healthy patients of primary care physicians and 100 cardiomyopathy patients and their physicians — to track a range of outcome measures. First, the team plans to design an informatics pipeline to interpret a whole genome's worth of variants and generate meaningful and interpretable clinical reports for physicians. They will then use this pipeline in the randomized trial.

The group hopes to identify weaknesses in the use of WGS in clinical care, discover where additional education of either the patient or physician might be needed to implement genetic information in healthcare decision-making, and establish successful methods for summarizing vast WGS data within the confines of routine doctor-patient meetings.

An especially important aspect of the project will be working to establish when and how to report "incidental" findings to patients, according to Robert Green, a BWH geneticist and the director of the study. The team will seek to find a middle ground between denying patients valuable information about disease risk on one hand and triggering unnecessary and costly medical tests on the other.

Green told *Clinical Sequencing News* that the BWH effort is the only project funded by the NHGRI's Clinical Sequencing program grant that is focused entirely on whole-genome sequencing. The team will be partnering with Illumina to send samples through the company's CLIA-approved process, Green said.

"I think it's only a matter of time before whole-genome [sequencing] is the norm," he said. "First, there are advantages to whole-genome sequencing in terms of coverage, because exome sequencing sometimes has difficulties at the beginnings and the ends of genes. Also, certain susceptibility variants — pharmacogenomic and otherwise — really are present in intronic areas and not just the genes themselves."

As a result, "we felt it was more visionary, more future-oriented, to try to go with whole-genome sequencing from the get-go," Green said.

The project is divided into a three-part structure, as required by the NHGRI's request for applications, Green explained. The first section, to create the protocol for the trial, is headed by co-principal investigators Mike Murray, chief of genetics at BWH, and Christine Seidman of the BWH cardiovascular division. The second section, dealing with the project's informatics, is led by Isaac Kohane, director of the informatics program at Children's Hospital Boston, and Heidi Rehm, head of the Laboratory for Molecular Medicine at Partners HealthCare.

Green and Amy McGuire, associate director for research at the Center for Medical Ethics and Health Policy at Baylor College of Medicine, co-head the third section, which is focused on the study's outcomes.

Green said that the main axis of the BWH project is to study whole-genome sequencing in the context of both primary care and specialized disease treatment.

"We decided there were two paradigmatic areas to wrestle with in terms of trying to integrate sequencing into medicine," he said. "One was if you have a presumed genetic disease and you are using sequencing to go chase it. For that we chose hereditary cardiomyopathy because it's a disease caused by mutations in [more than] 40 genes, [which means] sequencing is a reasonable and cost-effective way to go after the variants you think may be causing it in any patient or family."

The second area, which he said is "giving people fits," is the situation where otherwise healthy people want their genome sequenced to gain insight into their current or future health.

"To what degree can you search for, interpret, and report … findings in people who do not come to you with a prior probability of a genetic syndrome? This is the other sort of devilish problem in the application of sequencing to the practice of medicine," Green said.

In both groups, the BWH team will perform a trial where physician/patient pairs will be randomized to either standard care — which in the primary care group means no genetic testing, and in the cardiomyopathy group would mean "conventional genetic testing of the available genes" — versus care that is enhanced with the information from whole-genome sequencing, Green explained.

"We've set quite a big task for ourselves," he said, "because that means along the way, we have to decide which incidental findings we want to present, and how to present them in a meaningful report to the physician who will then interpret them to the patient."

Green noted that all the projects funded under the NHGRI's clinical sequencing grants will likely "have to wrestle with whether you don't give people incidental findings, give them a pre-set menu of findings, or give them some sort of choice or degree of preference as to what they would like to get back."

For the BWH project, Green's group made some "preliminary assumptions" regarding a limited set of incidental findings that it would return to patients. "We suggested some categories for that, but didn't specify what they would be," he said. "We left the tough work [because] part of what the grant will pay for is to help the talented people in the room make sensible choices about the kinds of variants that ought to be returned, perhaps whenever the genome is analyzed.

"This is very controversial ground and we're looking forward to struggling with those issues," he said.

The group plans to follow patients and doctors in the trial for a year, though many of the outcomes it is interested in — such as whether genomic information engenders anxiety in patients or increases medical workups or costs — will likely influence study subjects for several years after they receive sequencing information. "But, since we have to start somewhere, we're going to follow them for a year," Green said.

The group will soon hold its first retreat and plans to begin recruiting patients to the trial in the second half of 2012.

Green said that because his group is partnering with Illumina, it should avoid issues related to using in-house sequencing data for medical decision making.

"Illumina [is] at this moment in time, I think, the only entity that is actually doing CLIA-approved whole-genome sequencing," he said. "So, since we intend to use the results of this in the practice of medicine and return these results to ordering physicians, [it] seemed like the appropriate way to go."

"We are really trying to emulate how we think this is going to be used in the clinics of the future," Green continued. "I think whenever a new technology comes [along] … there are many people eager to use it. But that doesn't mean we understand its true benefits [and] how it should best be used."

Green said that while a number of hospitals and other groups are already beginning to incorporate genome sequencing into clinical care, the questions being asked in the NHGRI Clinical Sequencing Exploratory Research Project program are still crucial.

"I think it would be safe to say that those people who are [trying or are] going to use whole-genome or whole-exome sequencing in the next months or years are really pretty super specialized. They are people who have the capability to ask the right questions, analyze data," Green said.

"We really want to ask a more fundamental question: To what extent can whole-genome sequencing actually be useful broadly in the practice of medicine? And is that even possible?

"We think it is. And I think that's a huge challenge, if you will — to democratize sequencing without dumbing it down," he said.

In that sense, he said, the NHGRI is really "grabbing the bull by the horns and being very visionary in trying to collect data on this" issue.

"It's not that sequencing wouldn't take place without us," he said. "But I think this core group of projects will bring a scientific edge to the roll-out of clinical sequencing, which is going to help everybody."