At Genomics Festival, Brigham & Women's Researchers Discuss Early Findings from MedSeq

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NEW YORK – The first crop of data from a study at Brigham & Women's Hospital tracking how doctors understand and incorporate genomic sequencing results in their practice, shows that while they made some minor mistakes in communicating the data to patients, they learned and adapted to having this information as they would to any new tool.

The cost of whole-genome sequencing may be plummeting fast, but doctors don't have much use for a lot of the data that comes from such technology. When tests do reveal useful information, numerous surveys have found that doctors don't feel they have the expertise to incorporate it into patient care.

Within the MedSeq Project, researchers from Brigham & Women's and several other institutions wanted to figure out ways to support and educate non-geneticist physicians so they could incorporate genomic information into their patient's care.

Researchers within MedSeq began enrolling participants at Brigham & Women's in 2012 after receiving a four-year, $9.6 million grant from the National Human Genome Research Institute the prior year. At the Festival of Genomics in Boston this week, researchers reported the first data from the project showing that doctors performed more tests when they had patients' genomic information compared to when they didn't. They sometimes made mistakes in communicating genomic information to patients, but they improved their understanding over the course of the project and with support from MedSeq's genetics experts. Within this framework, so far, allowing doctors to discuss genomic information with patients and apply the information to guide care hasn't resulted in any catastrophic harm that some have feared.

The project has enrolled 102 cardiomyopathy patients who visited nine cardiologists and a similar number of healthy, middle-aged subjects who saw 11 primary care physicians. Patients in both the cardiology and primary care arms were randomized to receive the standard of care informed by family history information or standard of care informed by family history and whole-genome sequencing results.

Whole-genome sequencing found a previously unknown variant for a Mendelian disease for 21 percent of patients and a new carrier status in 92 percent of cases. In the cardiology arm, 13 percent learned of a new cardiomyopathy variant and 95 percent had a previously known cardiomyopathy variant confirmed by testing. In one case, whole-genome sequencing missed a large pathogenic deletion related to cardiomyopathy, but based on previous test results, the lab knew to look for this variant. For two patients with previously known cardiomyopathy variants, whole-genome sequencing identified a variant of unknown

After reporting the results to the doctor — including information on highly penetrant Mendelian mutations and recessive carrier status, pharmacogenomic associations, and blood group — researchers led by Robert Green of Brigham & Women's Hospital tracked the decisions doctors made, if the genomic information influenced additional testing or treatment strategy, and assessed how doctors conveyed the information to patients.

In order to participate in the project, physicians had to review 12 case scenarios online and listen to two in-person lectures, amounting to more than six hours of education. Green's team also created a Genome Resource Center, where doctors partaking in MedSeq could get advice from genetic counselors and medical geneticists about their patient's report. According to Brigham & Women's Joel Krier, one of the MedSeq researchers, some doctors said they felt overwhelmed after the six-hour education session, and 13 said they expected to use the Genome Resource Center, within which researchers hoped to support physicians but not overly influence or constrain their behavior.

In the past 28 months, however, Krier reported at the Festival of Genomics, the doctors didn't use the resource center as frequently as he had expected they would. To date, genetics experts at the resource center have had 12 consults with eight doctors, who are mostly primary care physicians. Five doctors have sought help from the resource center once, and three have asked for assistance on more cases.

Doctors who used the resource center have done so to check whether genomic testing would have picked up certain syndromes that occur in a patient's family; discuss treatment plans for patients in light of variants of unknown significance; and get advice on what to tell patients when they carry autosomal recessive markers and have adult children.

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One doctor was confused when a variant in the KCNQ1 gene associated with Long QT syndrome turned up in a patient's report as autosomal dominant and recessive. After a few email exchanges with experts at the Genome Resource Center, the doctor understood that this variant can be inherited in both an autosomal dominant and recessive pattern, and was able to advise the patient about the risk for Long QT syndrome, recommend an EKG, and refer the patient to see a cardiovascular geneticist.

"She handled the uncertainty of the situation quite well," Krier said. The doctor said she would continue to follow the patient in case Long QT syndrome became a problem in the future, and Krier felt she "provided good information without being overly alarmist."

MedSeq doctors documented the treatment or testing decisions they made and researchers reviewed these decisions, looking for errors or miscommunications about genetic concepts that resulted in wrong management strategies, and categorized them into three groups. The most severe are instances where the error has placed the patient in danger and requires immediate intervention to inform the physician and even the study safety board. Less serious are situations that require real-time feedback because the miscommunication could impact the patient's near-term healthcare decisions. Least concerning are scenarios where the patient isn't in any danger but physicians receive feedback at the end of the study to correct omitted or mischaracterized information.

So far, Krier's group has reviewed half of all the disclosures from doctors for around 97 patients. Of these, three cases required real-time feedback to correct doctors' misinterpretation of inheritance patterns and carrier risk, while 21 cases necessitated end-of-study feedback for minor errors. There were no serious mishaps that required immediate intervention, "and we hope this continues for the rest of the study," Krier said, adding that doctors might need more support in carrier risk counseling.

Although fewer physicians used the Genome Resource Center than expected, "some MDs may not have been willing to participate in our study without this safety net," and the resource center gave them "confidence to step into this unknown territory," Krier said.

In general, among patients who received genomic test reports, doctors ordered more labs, imaging tests, and cardiac tests compared to those who were treated without genomic information. In the primary care cohort, doctors changed medications for 16 percent of patients who received whole-genome sequencing compared to 4 percent of patients in the control arm.

At the Festival of Genomics, Green said that while genomic information will likely increase testing, it will be important to track what the value of that additional intervention is to the patient's health. Long term, MedSeq researchers will track the economic impact of using genomic information to care for patients.

In addition to MedSeq, Brigham & Women's is also involved in BabySeq, a project investigating the risks and benefits of genomic screening in healthy newborns and babies in the intensive care unit. The study, launched last year and led by Green and Alan Beggs at Children's Hospital Boston, has funding from the National Institute of Child Health and Human Development and NHGRI for 14 months. For most of that time, researchers have been refining the protocol, applying and responding to institutional review boards, and negotiating with the FDA about the design of the study.

At the meeting, Green said that three weeks ago researchers enrolled and sequenced the first newborn from the intensive care unit into BabySeq. Since then, researchers have enrolled a small number of families with healthy and ICU newborns.

Green also discussed at the meeting a third study called PeopleSeq, in which researchers will assess what people do after getting their whole genomes sequenced. So far, researchers have analyzed surveys from 70 out of nearly 300 people who received testing through Illumina's Understand Your Genome Program, and found that around 20 percent made an appointment with a healthcare provider, 10 percent got a medical exam or procedure, and less than 5 percent got a genetic test to confirm a variant identified by sequencing.

Most of the participants said they got sequenced out of personal or professional interest, but around a third said they got tested because they were concerned about a medical condition that runs in the family. Also a third of the respondents indicated they would consider sharing their results publicly with their identity attached, but around 4 percent said they wouldn't consider sharing it. Green's group plans to survey others who have gotten their genome sequenced through efforts such as the Harvard Personal Genome Project and the Mount Sinai HealthSeq Project.

Meanwhile, MedSeq is being carried out in a highly specialized academic medical center, where physicians are early adopters of genomic tools, and patients tend to be well educated and in a high-income bracket, Krier pointed out. As such, a similar project at a community practice, for example, may reveal different challenges when doctors treat patients in the context of genomic information.

Still, the MedSeq experience suggests to Krier and his group that doctors are learning quickly and adapting to having genomic sequencing results as they would to any new information or tool. "[MedSeq] is not meant to be a scalable study with materials we can roll out to everyone," he said. "But our study is beginning to show some reassurance that disaster may not imminently strike when non-geneticist physicians get involved in returning genomic information to patients."

Filed Under Sequencing Genetic Research Brigham and Women's Hospital whole-genome sequencing