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Preventive Genome Screening Hot Topic at ACMG Meeting

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NEW YORK (GenomeWeb) – Exome and whole-genome sequencing have been firmly established as diagnostic tools for rare genetic diseases that can pinpoint molecular causes missed by more targeted tests. More recently, though, several labs have started to move genome-scale sequencing into preventive medicine, with the goal to detect increased disease risks and predict atypical drug responses in seemingly healthy individuals.

At the American College of Medical Genetics and Genomics annual meeting in Phoenix, Arizona, last week, representatives from Harvard Medical School, Illumina, Baylor College of Medicine, the HudsonAlpha Institute for Biotechnology, and the National Human Genome Research Institute talked about their experience with genomic tests catering to individuals that neither have cancer nor a rare inherited disorder, variedly referred to as "genome screens," "elective genomes," or "narcissomes." In addition, several commercial labs spoke about recently launched or planned genomic tests for so-called healthy adults at the conference, including WuXi NextCode, Ambry Genetics, and Invitae.

According to Les Biesecker, who has been involved in predictive genome sequencing since about 2007, when the NHGRI's ClinSeq study started analyzing the genomes of adults from the general population in the Washington, DC area for specific disease risks, genome-based clinical screening "is going to happen," which he said does not mean it is necessarily medially indicated. "We cannot stop it," he said.

One question the community has been asking is whether primary care physicians will be able to use genomic information appropriately and whether this would lead to increased healthcare costs from follow-up tests they might order. The MedSeq Project, conducted at Harvard Medical School and funded under the National Institutes of Health's Clinical Sequencing Exploratory Research program, has been conducting a randomized controlled trial involving nine primary care physicians and 100 patients. Half of them were assigned to discuss their family history with their doctor, the other half to talk about family history and a whole-genome sequencing report.

According to Jason Vassy, one of MedSeq's principal investigators, "with support, primary care physicians may be able to manage genome sequencing results appropriately."

Of the 50 patients who received whole-genome sequencing under MedSeq, 11 had a monogenic disease risk variant, which was the first item presented to their doctors in their clinical genome report. Interestingly, two of these patients had symptoms consistent with the phenotype of the disease — in

one case, a retinal disease, in the other, a skin disorder — but had not been formally diagnosed before.

Doctors ordered a number of tests and referrals to specialists for patients with positive results, Vassy said, but only cardiology tests reached statistical significance over the control arm. Overall, 34 percent of patients with genome reports had some kind of clinical action taken, whereas 16 percent of patients with only family history did. After six months, patients who had undergone genome sequencing had racked up about $350 more in healthcare costs from tests and referrals than patients who had not, but Vassy said the numbers were too small to be statistically significant.

The researchers also evaluated how well doctors managed the genome results, using the RAND Appropriateness Method and expert ratings, and found that in most cases, they took appropriate actions, though there was concern about one case where a doctor did not further investigate a pathogenic mutation for combined pituitary hormone deficiency.

With sufficient education and support, including just-in-time resources, primary care doctors were able to manage genome sequencing results, Vassy concluded.

While MedSeq has been sequencing ostensibly healthy individuals as part of a research study, Baylor College of Medicine and the HudsonAlpha Institute have seen clinical exome or genome scans for healthy adults grow out of their diagnostic programs for patients with rare genetic diseases.

Healthy genome tests might not be all that unusual, given that asymptomatic individuals already receive other types of genetic tests today, such as genetic cancer risk screens, carrier disease testing, and pharmacogenetic tests, said Christine Eng, chief medical officer and chief quality officer of Baylor Genetics, Baylor's clinical genetics diagnostic laboratory. On the other hand, according to Kelly East, a genetic counselor at HudsonAlpha, "it is striking how not-healthy our healthy patient population is."

Baylor started offering non-diagnostic exomes in 2013 and has received samples from 37 individuals so far, Eng reported. The test needs to be ordered by a physician and is available to patients 18 years or older who do not have a rare genetic disorder or a family history of one. It reports pathogenic or likely pathogenic variants in genes related to diseases with clear medical significance to the patient's own health or that of their family, she said, in addition to disease carrier status and limited pharmacogenetic results for the drugs warfarin and clopidogrel (Plavix). Variants of unknown significance may be reported if the patient or their family has a history of an associated condition, she added.

Of those seeking the test, 20 reported having a medical condition, and 10 noted a family history of diseases such as cancer, coronary artery disease, or diabetes. Several had a deceased child in whom no genetic disease had been diagnosed.

All but one patient turned out to be carriers of at least one genetic disease, and on average, patients had slightly more than two carrier results. Also, 35 out of the 37 patients had a pharmacogenetic result indicating altered drug metabolism, which Eng said was higher than expected. A few had diagnostic findings in disease genes that in some cases made sense with their symptoms.

As part of its diagnostic exome program, Baylor often also sequences the exomes of unaffected family members, Eng said, and offers to report secondary findings in the ACMG-recommended gene list in these patients, which 94 percent have accepted. The prevalence of such findings has been about 2.5 percent in probands and nearly 2 percent in unaffected parents, she said, most commonly in genes related to cardiac disease and cancer.

The HudsonAlpha Institute recently launched a whole-genome sequencing service for healthy individuals, called Insight Genome, which grew out of its diagnostic whole-genome sequencing service. Of the first 24 patients enrolled for the new test, seven received a primary result related to their phenotype, one had a secondary finding, and 17 were found to be carriers of a genetic disorder, said David Bick, the institute's chief medical officer. In addition, half of the participants had pharmacogenomic findings that affect the metabolism of at last three drugs.

As an example of a carrier screening result that has wider implications, Bick pointed out a patient who was found to have a variant in the ATM gene, making him not only a carrier of ataxia telangiectasia but also increasing his risk for gastrointestinal cancer, so he is now under increased surveillance.

Bick said he favors the term "elective genome" for genome tests of healthy individuals, but others objected to this term, arguing that it implies such a test would never have medical utility or be covered by health insurance. Bick countered, however, that *in vitro* fertilization also started as an elective procedure but is now often paid for by insurance.

Another concern clinicians have had about genome-wide testing in healthy people is the large number of variants of unknown significance, or VUS, that such testing may generate, and most services do not report those variants at the moment.

But the status of variants can change over time, according to Erica Ramos, clinical head of Illumina's Healthy Genome Initiative. Since 2012, when Illumina first started offering whole-genome sequencing with a clinical interpretation of about 1,700 genes, Illumina has analyzed the genomes of almost 1,300 participants in its "Understand Your Genome" program, among them more than 1,000 in the US, she said.

As of last year, the company had called a total of 54,000 VUS, but when it reclassified them using frequency data from the Exome Aggregation Consortium (ExAC), about 10,000 of these variants moved into the "likely benign" or "benign" category. At the same time, a significant number of variants originally classified as "VUS suspicious" moved to "pathogenic" or "likely pathogenic", so there might be some value in reporting those initially to allow doctors to keep an eye on them, Ramos said.

Several healthy genome screening efforts are also grappling with how to provide pre- and post-testing counseling services to a growing number of participants and are exploring new ways for doing so. Hudson Alpha's East, for example, reported that her institute provides online educational material ahead of the patient's visit and assigns topics most relevant to them for reading. However, she said that only about a fifth of the "elective genome" patients read through all of the assigned topics, and more than two thirds read none of them. Pre-test visits to the clinic still took an average of an hour and a half, she noted, and post-test visits, which can be done by phone or video conference, average almost an hour.

Likewise, Baylor is also developing educational videos and web-based counseling services as a way to address the shortage of counseling resources as testing volumes pick up, Eng said.

Another often-voiced concern is that genomic testing for wellness purposes is currently mostly available to and used by a demographic of well-educated and wealthy individuals and is not available to the general population, and most of the current services bear this out. Participants in the MedSeq project, for example, are overwhelmingly affluent, of European ancestry, and highly educated, according to Vassy. Likewise, almost all of HudsonAlpha's Insight Genome customers have at least one advanced degree and 92 percent are Caucasian, according to East.

In an effort to change those demographics, Illumina in late 2015 partnered with the San Diego Blood Bank for a community-driven genomics research study that at the time aimed to sequence the genomes of up to 100 volunteers. The cohort turns out to be very diverse and includes many Latinos, Ramos said, and participants are "highly engaged."

Other commercial laboratories also appear to be jumping onto the preventive genome screen bandwagon. WuXi NextCode, for example, presented results from a pilot study of a whole-genome sequencing scan called HealthCode at last week's ACMG meeting, which it introduced in China last year.

Also, Ambry Genetics said last week that it is embarking on a pilot study for a planned exome sequencing service for healthy individuals and seeks to involve genetic counselors as alpha testers. According to a spokesperson, the company plans to consider feedback from the genetics community, and from physicians and clinics who might use the test. "We are hoping the pilot study will help us to fine-tune the categories of information we report," the spokesperson said in an email. Ambry is currently vetting a list of genes for medically relevant findings in the areas of cancer, cardiology, neurology, family planning, and pharmacogenetics and also plans to include the ACMG-59 gene list for secondary findings.

Finally, Invitae said last week that it has added new tests to its proactive genetic testing pilot program, called Invitae Genetic Health Screen, and the firm presented several posters related to the program at ACMG. The screen currently analyzes 139 genes related to inherited cancer, cardiovascular disease, and other conditions and reports results with a "clear medical basis" that are clinically actionable. Invitae said the tests are intended for patients who do not meet diagnostic criteria for genetic testing but want to use genetic information to inform health-related decisions. It said the program has been available at several clinical pilot test sites for more than a year and more sites will be added this year.

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