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# Clinical Exomes Take Off: UCLA Launches Dx Test, Ambry Reports First Successful Results

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By [Monica Heger](#)

**As exome sequencing** quickly becomes the method of choice for diagnosing rare conditions, a number of academic groups and companies have launched tests in recent months and are reporting their first successes.

The University of California, Los Angeles, is one of the newest groups to offer exome sequencing in a CLIA-certified laboratory. Currently, it is running the test on the Illumina HiSeq 2000 using either Illumina's TruSeq exome capture kit or Agilent's SureSelect, and sequencing to 100-fold.

UCLA is targeting its test to patients with rare Mendelian diseases. It offers the service at \$4,500 for an individual, \$6,500 for a trio of exomes, and \$2,500 for each additional exome. Turnaround time is about 12 weeks.

"There's a very large number of people with a clear Mendelian disease that do not have a molecular diagnosis," Stan Nelson, a professor of human genetics at UCLA, told *Clinical Sequencing News* at last week's Future in Genomic Medicine conference at Scripps Translational Science Institute.

In contrast with other academic institutes that use sequencing as a last resort for patients who have already endured a diagnostic odyssey, Nelson said that his theory is to sequence first.

There are currently 1,700 different genetic tests for around 3,000 different disorders, he said. "It's clearly more efficient to sequence the exome first, as the first genetic test," rather than subject a patient to a whole host of different tests, he noted, though he acknowledged that there are exceptions in cases that are relatively straightforward.

There are not a lot of limits on the types of patients who would be eligible for exome sequencing, he said. "Anyone with a very rare serious phenotype that's likely to be a single genetic event" would be eligible, he said.

The UCLA team has about 60 cases in the pipeline, one of which they have sequenced, analyzed, and found a diagnosis for. While in the process of setting up the service, the team found diagnoses for 12 other cases.

On average, Nelson said that they find a molecular cause in about half of the patients.

Following the sequencing, an informatics approach is used to filter for variants likely to be involved in the gene. The approach looks for variants in a series of different disease models, such as, rare autosomal recessive, *de novo* autosomal dominant, and X-linked recessive. Those variants and genes are then highlighted for further evaluation by a genomic data board.

Expert physicians, genetic counselors, bioinformaticians, medical geneticists, and the patient's primary physician all sit on the board and discuss the results.

The board receives results that have been filtered with the informatics pipeline to include a candidate gene list. Only results that are relevant for the patient's disease are returned. The test is "explicitly to diagnose," Nelson said.

While the UCLA team is more permissive in terms of determining which patients qualify for the test, they are more conservative than others in terms of what results to return. For instance, the Medical College of Wisconsin and Children's Hospital of Wisconsin, which have a clinical whole-genome sequencing protocol for children with rare diseases, will return any relevant results that the patient's parents want, including variants that confer risk for adult-onset diseases (*CSN 3/29/2011*). However, the MCW team is more stringent about what patients it sequences — using the sequencing only after all other options are exhausted.

While UCLA currently has no formal agreements with payors about reimbursement, it will help patients make a case to insurance companies, and Nelson said that he thinks the test will eventually be reimbursed, because it will ultimately save money.

Compared to the "old-fashioned route" of working through a series of single-gene tests, which could ultimately cost upwards of \$20,000 and still not yield a correct molecular diagnosis, doing exome sequencing first is a "very compelling argument" to make to insurance companies, he said.

The first clinical case that was sequenced at UCLA was reimbursed. In that case, the team sequenced a child that had, among other problems, severe developmental delays. Exome sequencing identified a *de novo* point mutation in a gene to which heterozygous mutations were shown to cause Pitt-Hopkins syndrome, a rare disorder characterized by intellectual disability, abnormal breathing, and distinctive facial features.

Despite this early success, Nelson said that it is important not to overpromise, adding that of all the cases that the UCLA team has sequenced in a research setting, it's only diagnosed about half. Additionally, while he is a proponent of sequencing for most cases of genetic rare disease, he acknowledges that there are still some challenges associated with interpretation as well as other factors, such as not having enough clinical phenotypical data on the patient.

For instance, he said, within a research setting, the UCLA researchers sequenced a girl who had been diagnosed with juvenile amyotrophic lateral sclerosis. Exome sequencing turned up potential variants to a gene known to be involved in another rare disorder known as Achalasia-Addisonianism-Alacrimia syndrome. Patients with that disorder typically have trouble swallowing and don't produce tears.

At first look, this did not appear to be the causal mutation because the clinical presentation didn't match, Nelson said. But it turned out that a subset of patients with triple-A syndrome also have juvenile onset spinobulbar muscular dystrophy, which can look like ALS. Additionally, further questioning of the patient uncovered that she had never cried.

Based on this evaluation, the exome sequencing turned out to have identified the correct gene, and the initial diagnosis of juvenile ALS was not correct, Nelson said.

Despite these challenges, Nelson said he thinks exome sequencing for rare diseases is ready for the clinic, and will serve as the "wedge" that drives sequencing into the clinic more broadly.

### **Ambry Reports First Success**

Ambry Genetics, which launched an exome sequencing test last fall, has had some early successes, providing three diagnoses from individuals from four different families.

In one case, the test, conducted in conjunction with the Kennedy Krieger Institute in Baltimore, provided a molecular diagnosis for two brothers with a severe form of intellectual disability and cerebral palsy. The test found that they each had two rare mutations in the ELP2 gene — one inherited from their mother, one from the father. The brothers are now in their 20s, and the family did not think they would ever find a molecular diagnosis.

Cathy Rzepowski, the mother, told *CSN* that even though the diagnosis will not lead to a treatment for her sons, it has given her closure. "Over the years, I always thought it was my fault," she said.

Additionally, she and her husband have two other children: a son who is married and has two healthy children; and a daughter, who is married, but does not yet have children. They also had their exomes sequenced, and the test found that the son was not a carrier of either mutation, but that the daughter was a carrier.

Rzepowski said that this information was also a relief to know. While her daughter is of course not happy about having the mutation, she said that she understood that despite having the mutation, the chances of having children with the same disorder was still low.

Additionally, she said that while the information relevant to her sons' disease has already been returned, the family is going back to the genetic counselor to discuss the return of other relevant findings. She said, in her case, she would want to know anything, even risk variants for diseases like Alzheimer's. "I think it's good to know what else there could be," she said. "It gives you a heads up."

Julie Neidich, Ambry's medical director, told *Clinical Sequencing News* that the company decides on a case-by-case basis whether to report medically relevant findings that are not related to the patient's disease. Currently these reports are performed as a secondary analysis if the family wants that data.

"Our first aim is to make sure we find something that's diagnostic for the family," she said. Additionally, there are constraints about what the company will report depending on the patient's age. For instance, Ambry will not report variants for adult-onset diseases in children under 18.

Of the cases that Ambry has diagnosed so far, Neidich said that they were all cases that would not have been immediately obvious. For instance, for Rzepowski's sons and another case of severe intellectual disability, there are hundreds of genes that impact intellectual disability, she said. So trying to figure out the one causative one could potentially be extremely time consuming and costly.

In the third case, Neidich said that the clinical presentation suggested some 200 genes that could have been involved, and that the disease was likely caused by multiple genes. In that case, simply doing exome sequencing was more cost-effective than trying to design a panel of one to 10 genes.

"The family was interested in finding therapeutic clinical trials for the affected family member, so they wanted to go for the most diagnosis-potential, the most wide-ranging path they could get, in the shortest

amount of time," she said. The sequencing did yield results that would potentially make the patient eligible for a clinical trial, and the family is now in the process of applying to trials, she added.

Ambry is still analyzing results from the other patient samples it has sequenced. The company would not provide exact numbers but said it is receiving samples every day.

Additionally, Neidich said that Ambry is receiving reimbursement for the test on a case-by-case basis, although she could not provide specifics about what insurance companies were reimbursing.

Exome sequencing to diagnose rare disease is gaining ground in genetics labs everywhere. Aside from UCLA and Ambry, Washington University's School of Medicine recently said it plans to start offering a clinical exome sequencing service through its Genomics and Pathology Services division ([CSN 2/29/2012](#)). And, according to Emory Genetics Laboratory's website, it is gearing up for a clinical exome sequencing service. The CLIA-certified lab already offers next-gen sequencing-based tests for intellectual disability and congenital metabolic disorders.

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