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Exome sequencing offers diagnostic clarity that can guide care decisions

Gene sequencing capabilities have advanced impressively over the past decade and the technology is beginning to have a significant impact as a diagnostic tool. In 2001, the first draft of the human genome was sequenced after a 10-year effort that cost about $3 billion. By 2007, the first individual genome sequence was published. It took about six months and cost about $4 million. Today, next-generation sequencing tools make it possible to sequence the protein-coding portion of a patient's genome — and that of both parents — in a few weeks at a cost of about $6,500.

Nearly all of the over 3,000 Mendelian genetic diseases — those caused by mutations in a single gene — are due to changes in a protein-coding sequence. The protein-coding portion of the genome, known as the exome, consists of about 30 million bases, or just 1 percent of the 3 billion bases that make up the 23 chromosomes of human DNA. Exome sequencing has become an efficient way to establish a diagnosis in a wide range of diseases where genetics is a major contributor.

Benefits of genetic diagnosis

There are many reasons to pursue genetic diagnosis. Parents of young children with serious medical issues can endure months or even years of diagnostic uncertainty that may never resolve into a completely satisfactory diagnosis. For couples planning their families and their futures, the high clarity of genetic information can be very impactful.

New diagnostic tool should be used early

"With recent technology improvements, exome sequencing is poised to make a striking change in diagnostic medicine," asserts Stanley F. Nelson, M.D., professor of human genetics and pathology and laboratory medicine. Rather than turning to genetic testing only when unable to otherwise establish a diagnosis, physicians should consider exome sequencing a first option for diagnosing conditions that are likely to have a genetic component.

Next-generation sequencing tools provide the means to very rapidly sequence the protein-coding portion of an individual's genome. UCLA experts can interpret every variant to determine the causal mutations that are responsible for a patient's disease.

While there is no treatment to reverse the genetic mutation, genetic diagnosis is valuable for the way that diagnostic clarity can alter the approach to managing previously ambiguous cases. It can also alert physicians to related syndromes that may have been overlooked whose treatment can offer some relief to patients. "By using sequencing very early in the diagnostic process, we can guide the diagnostic work-up in a very powerful way," asserts Dr. Nelson.

Genetic diagnosis can also enhance patient care by alerting physicians to the possible presence of other conditions known to accompany the underlying mutation. An accurate diagnosis can sometimes suggest the presence of additional, often treatable, syndromes known to accompany the primary condition. Exome sequencing can dramatically alter how the physician views and cares for the patient.

Modern exome sequencing

Next-generation sequencing technology has helped to make exome sequencing vastly more efficient than older genetic testing options. Previously, physicians would try to deduce individual genes for testing based on their examination of the patient. But matching medical problems with gene mutations has proven to be extremely difficult, often leading to a series of negative results followed by more clinic visits and more negative results.

By testing the entire exome at once, experts can interpret every DNA change in the individual's exome and determine the causal mutations that might be leading to that patient's disease. Exome sequencing can save considerable time and money by reducing clinic visits and eliminating unnecessary tests, including more invasive procedures. Most medical insurance will reimburse for sequencing to diagnose a serious Mendelian genetic disease.

The success rate of causal gene identification is about 50 percent even for disease cases that have been thoroughly evaluated prior to referral for clinical exome sequencing. The technology is best applied by sequencing the mother, father and affected individual, but many instances of successful disease gene identification have been accomplished by sequencing only the affected individual.

UCLA's exome sequencing program

UCLA's Clinical Exome Sequencing team includes experts in pediatrics, pathology, molecular genetics, medical genetics, bioinformatics and sequencing technology whose collective experience contributes to the high precision of the gene sequencing and insightfulness of the interpretation.

On average, an individual exome will contain about 22,000 DNA variants from the reference human genome, but few of these variants will affect the person's health. Identification of the causal mutation or mutations requires careful interpretation of the DNA variants by UCLA's expert team in light of the patient's medical problems.

When the team is unable to identify the causal mutation, the sequencing data is saved for future reinterpretation. As research links more gene mutations to genetic diseases, the sequencing data can be reinterpreted in an attempt to identify the causal mutation and establish a genetic diagnosis.

UCLA's Clinical Exome Sequencing program includes genetic counseling to help patients and referring physicians use the information that exome sequencing provides and understand the implications of the data. UCLA is currently the only major medical center in California that offers an exome sequencing service.

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You'll also find a variety of resources at our website — *www.pathology.ucla.edu/genomics* — including everything you'll need to submit a request for exome sequencing.