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Study examines type of exome sequencing and molecular diagnostic yield

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In a sample of patients with undiagnosed, suspected genetic conditions, a certain type of exome sequencing method was associated with a higher molecular diagnostic yield than traditional molecular diagnostic methods, according to a study appearing in *JAMA*. The study is being released to coincide with the American Society of Human Genetics annual meeting.

Exome sequencing, which sequences the proteincoding region of the genome (the complete set of genes or genetic material present in a cell or organism), has been rapidly applied in research settings and recent increases in accuracy have enabled the development of clinical exome sequencing (CES) for mutation identification in patients with suspected genetic diseases. Early in 2012, the Clinical Genomics Center at the University of California, Los Angeles, launched a CES program with the goal of delivering a more comprehensive method for determining a molecular diagnosis for patients with presumed rare Mendelian disorders (a genetic disease showing a certain pattern of inheritance) that have remained undiagnosed despite exhaustive genetic, biochemical, and radiological testing. Researchers at this center have introduced a new test, called trio-CES, in which the whole exome of the affected proband (first identified individual affected with the disorder among other family members) and both parents are sequenced, according to background information in the article.

Hane Lee, Ph.D., of the University of California, Los Angeles, and colleagues report the results of clinical exome sequencing performed on

814 patients with undiagnosed, suspected genetic conditions at the Clinical Genomics Center between January 2012 and August 2014. Clinical exome sequencing was conducted as trio-CES (both parents and their affected child sequenced simultaneously) or as proband-CES (only the affected individual sequenced) when parental samples were not available.

Overall, a molecular diagnosis (with the causative variant(s) identified in a well-established clinical gene) was provided for 213 of the 814 total cases (26 percent). There was a significantly higher molecular diagnostic yield from cases performed as trio-CES (127 of 410 cases; 31 percent) relative to proband-CES (74 of 338 cases; 22 percent) in the overall group of cases.

In cases of developmental delay in children (