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CLINICAL GENETICS

Exomes in the clinic

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A new study provides the largest survey so far of the use of exome sequencing for clinical diagnosis.

Yang *et al.* report results for the first 250 individuals to undergo clinical exome sequencing at the Baylor College of Medicine, Houston, Texas, USA, following referral by a physician. Most of the patients (222) were under 18 years of age, and most had undiagnosed disorders that involved neurological symptoms.

In 25% of cases, a positive diagnosis was made following exome sequencing — a proportion that is consistent with rates from smaller studies. This rate is higher than those for other types of genetic tests. Notably, before exome sequencing was ordered for the patients in this study, extensive efforts at diagnosis had been carried out, and in some cases this had taken longer and had cost more than whole-exome sequencing.

The authors suggest that the identification of new disease–gene associations and improvements in the detection of copy-number variants will increase the success rate of exome sequencing. However, they also note important limitations to the approach, for example, the possibility that many causal variants may lie in non-coding regions of the genome.

A much-discussed aspect of clinical exome sequencing is the finding of medically actionable variants other than those that are directly related to the phenotype under investigation. Such incidental findings were made for 30 of the 250 patients, which underlines the importance of considering when and how such findings are relayed to patients and their physicians.

Altogether, the findings reported in this study provide a useful basis for considering how exome sequencing should be most effectively applied as its use becomes more widespread.

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ORIGINAL RESEARCH PAPER Yang, Y. *et al.* Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1306555 (2013)