# Molecular Pathology Selected Abstracts, 2/15

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## Exome and genome sequencing for neurodevelopmental disorders

Neurodevelopmental disorders, which affect more than three percent of children, are associated with a variable type and acuity of presentation, ranging from global developmental delay, to autism, to intellectual disability. Although a genetic cause underlies many neurodevelopmental disorders, current standards of care using multiple imaging, metabolic, and serial molecular diagnostic approaches provide a definitive etiologic diagnosis in fewer than 50 percent of cases. The frequent result of these costly and time-consuming efforts is uncertainty regarding the cause of the disorder, most appropriate treatment for it, and risk of recurrence. The recent transition of whole exome sequencing (WES) and whole genome sequencing (WGS) to the clinical laboratory setting is widely viewed as having the potential to revolutionize the ability to diagnose such disorders in a timely and cost-effective manner. The authors' experience with these technologies provides evidence that the diagnostic paradigm for neurodevelopmental disorders may soon be altered significantly. The authors evaluated 100 families with 119 children affected by such disorders using WES or WGS, or a combination of the two, based on acuity of illness. For infants acutely symptomatic at birth or shortly after birth (n=16), an expedited WGS procedure was employed, providing diagnostic results within an average of 64 days or, in some cases, in as little as six to 10 days. For children being followed in ambulatory care clinics (n=103), a nonexpedited WES procedure was used, followed by WGS if WES was not informative. Time to diagnosis for these cases averaged 11.5 months. To the extent possible, parent-child trios were tested, with an average of 2.55 individuals per family being evaluated. Overall, a definitive molecular diagnosis of an established genetic disorder was obtained for 53 of the 119 children, or 45 of the 100 families. Seventy-three percent (11 of 15) of families with acutely ill infants received a definitive diagnosis by expedited WGS, while 40 percent (34 of 85) of families with children followed in ambulatory care clinics, in which the children had been refractory to diagnosis by traditional techniques, received definitive diagnoses by either method. Significantly, in 49 percent of cases (22 of 45 families), the diagnosis led to a change in patient management or clinical impression of the pathophysiology. In addition to the 45 definitive diagnoses, potentially pathogenic variants in candidate disease genes were identified in nine other families, which, through validation studies, may reveal new disease genes. Finally, the authors conducted a financial analysis in which the cost for laboratory testing using traditional diagnostic approaches was compared with the cost of using WES or WGS for diagnosis. Factoring in the average cost for testing trios when using WES or WGS and an average rate of diagnosis of 40 percent, the authors concluded that their diagnostic strategy would be cost-effective at a price point of $2,996 per individual. Of note, this comparison does not account for the anticipated cost savings afforded by a more rapid diagnosis in terms of decreased numbers of physician visits and other ancillary health-management expenditures. Although this cost per test may be lower than achievable for the performance of WES or WGS in a typical clinical laboratory, the downward trend in sequencing costs makes it a realistic expectation for the near future. As a whole, this analysis provides valuable evidence supporting the clinical benefits and probable cost-effectiveness of using strategies employing WES and WGS for the diagnosis of neurodevelopmental disorders.

Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med*. doi:10.1126/scitranslmed.3010076.

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