Greenberg et al provide a systematic review and meta-analysis to examine the diagnostic yield of exome sequencing (ES) in patients with congenital hydrocephalus (CH). A positive ES was defined as detection of pathogenic and likely pathogenic variants, as opposed to detection of variants of uncertain significance, likely benign variants, benign variants, or no variants. Their review identified 538 probands from 9 studies published since 2010, with an overall diagnostic yield of 37.9%. Subgroup analyses identified higher yield among those with actual CH vs those with only ventriculomegaly (43.2% vs 27.9%) and a higher yield for CH and ventriculomegaly probands with reported history of consanguinity than those without (76.3% vs 16.2%). The yield for CH and ventriculomegaly probands was also lower for isolated and/or nonsyndromic cases (21.3%).

Based on these data, the authors suggest broader use of ES in the early management of CH, especially among patients with consanguinity and prenatal severe ventriculomegaly. They also suggest that even though a gene panel is usually sufficient to establish a diagnostic yield in syndromic cases, ES might provide complementary and additional information.

This study further opens the door to a new era in our understanding and management of CH. For decades, the focus of those of us who treat this condition has been on incremental improvements in our downstream surgical treatment, which has included minimizing complications of cerebrospinal fluid diversion shunts and, more recently, exploring the role of endoscopic treatment as a shunt alternative. It is now becoming evident that our understanding of CH needs to go beyond the mechanical pathophysiology to the genetic basis that often underlies this condition. This is the case with many other conditions. In fact, Greenberg et al acknowledge that the impetus for their study was the recent American College of Medical Genetics and Genomics clinical guidelines recommending ES for those with a range of neurodevelopmental disorders, for which they report a diagnostic yield of 38%. The authors of the guidelines also noted the perceived beneficial value that parents place on even negative results. These guidelines, however, excluded CH. With the data now provided by Greenberg et al, an argument can reasonably be made to include certain cases of CH and severe ventriculomegaly for consideration of ES.

As noted by Greenberg et al, however, the use of ES has resource and financial implications that will resonant differently in different settings. The global burden of CH is large, and it disproportionately falls on low-income and middle-income countries where ES testing is largely not practical. As well, notwithstanding the knowledge that can be gained by more widespread ES testing, it is not clear how many of these results will be actionable from a medical or family planning perspective. As ES becomes used more widely used for CH, the direct impact of testing on children and families will need to be evaluated. Regardless of these caveats, this work by Greenberg et al reminds us that we have much to learn about the basis of CH, and by expanding our understanding, one hopes we will also improve the care of these children around the world.
REFERENCES


