

Title: From Last Resort to First Choice: The Ascension of Exome Sequencing in Isolated NDD Diagnostics

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Objective: Historically, exome sequencing (ES) was used for complex, multisystem cases that remained undiagnosed after other testing methods. While professional guidelines now recommend ES as a first-tier test for neurodevelopmental disorders (NDD), many clinicians still opt for multigene panel tests (MGPT). This study aims to delineate the clinical characteristics of patients undergoing ES and assess the diagnostic outcomes compared to MGPT.

Methods: We performed a retrospective analysis of cases undergoing ES at a single clinical laboratory. Clinical records provided at the time of testing were mapped to Human Phenotype Ontology (HPO) terms. Based on the comprehensive set of assigned HPO terms, cases were categorized as 'isolated NDD' (n=2244) and 'multisystem NDD' (n=1742) for analysis. Ordering trends and diagnostic yield for ES and MGPT were evaluated.

Results: Between 2018 and 2023, the proportion of ES tests conducted annually for isolated NDD cases exhibited a 37% relative increase (from 27% to 37%), while multisystem NDD had a relative decrease of 29% (29% to 20%). Isolated NDD emerged as the most prevalent clinical category ordered for ES in 2023. Comparing diagnostic rates between MGPT for NDD and ES, there was a significantly higher diagnostic rate ($p < .0001$; OR 0.442 95%CI: 0.3629 to 0.5832) and lower rate of variants of uncertain significance (VUS; $p < .0001$; OR 0.058 95%CI: 0.2976 to 0.4156) for ES compared to MGPT.

Conclusion: The shifting trend towards ordering ES for isolated NDD reflects evolving clinical practices. ES demonstrates improved diagnostic yield and lower rates of VUS compared to MGPT for NDD, underscoring its utility as a first-tier diagnostic tool in neurology.