**Variable Rates of Reclassification Based on Clinical Indication among Patients Referred for Diagnostic Exome Sequencing**

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Diagnostic exome sequencing (DES) is successful in providing a molecular diagnosis for ~25% of patients with underlying Mendelian diseases. DES has the potential to end the expensive, invasive, time-consuming testing and lead to changes in patient care. A major benefit of DES is the simultaneous interrogation of virtually all genes, including those recently characterized as disease causing. Reclassification of DES reports occur due a variety of reasons including subsequent familial co-segregation analysis, new patient clinical information, bioinformatics pipeline upgrades, variant reclassification, and new gene-disease information. Publications about gene-disease discoveries occur every two to three days on average, making reclassification due to new gene information the most common reason for a reclassification DES report.

We calculated overall reclassification rates among 6027 DES patients. Patients are grouped into one of 29 clinical indication categories prospectively as they arrive for testing. A reclassification was defined as any change to the overall results category among the following four groups: negative, positive/likely positive, uncertain findings within characterized genes, and candidate findings within uncharacterized genes. Reclassifications from candidate or uncertain to negative or positive/likely positive to any other category were considered downgrades and all other changes were considered upgrades.

Among 6027 DES patients, 2.3% (138) received a reclassification report; 2.0% (121) of which were upgraded and 0.3% (17) were downgraded reclassifications. The highest rates of reclassification were among patients with primary indications of hypotonia (6/80; 7.5%), abnormal muscle biopsy (1/17; 5.9%), ataxia/spasticity (5/103; 4.9%), cancer susceptibility (3/71; 4.2%), skeletal disorders (7/187; 3.7%), and intellectual disability (14/380; 3.7%). There were no reclassifications among patients within eight clinical categories including psychiatric disease, muscular dystrophy, overgrowth, hematologic disease, endocrine disease, respiratory disease, gastrointestinal disease, and otolaryngology.

The variable rates of reclassification are likely a reflection of the rates of new gene-disease discoveries and appear to be enhanced among more heterogeneous conditions. These dataset represent the largest group of DES patients analyzed for rates of reclassification to date. The data highlight the utility of DES in providing a comprehensive and timely molecular diagnosis with the ability to continually assimilate new gene discoveries. The data also emphasize the importance of counseling patients about the likelihood of a result reclassification in the future.