

## Diagnosis rate of Clinical Exome Sequencing and Whole Exome Sequencing in rare diseases: A comparative approach

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Rare Diseases (RD) are a large group of highly heterogeneous disorders, defined according to incidence. Given their rarity and complex manifestations, many patients remain undiagnosed for several years. These are considered Rare Undiagnosed Diseases (RUDs). To generate discoveries on novel causes of RUDs in the context of a country with limited genomic resources, we developed a pilot program for patients with unknown diagnoses.

In this report compared the diagnostic yield of proband-only NGS alternatives, including Clinical Exome Sequencing (CES) (approximately 5000 known disease-causing genes) and Whole Exome sequencing (WES), vs WES in family trio strategy using commercially available bioinformatics analysis algorithms. These processes were followed by multidisciplinary team variant interpretation.

To date, a total of 39 patients with RUD have participated in the study; 15 patients had CES, 25 had WES (10 with previous CES testing) and 9 patients had WES trio family analysis. The global rate of variant detection was 53.8%. These preliminary results twice higher diagnostic yields for WES (50% overall) compared to CES (26%) in this group of patients. The yield of WES trio family analysis was higher than WES- and CES-proband only (67, 44 and 26%, respectively). A predominance of *de novo* variants in the diagnosed cases was observed. The results show the feasibility of developing a local undiagnosed diseases program in Chile.

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