The Hospital for Sick Children
Technology Assessment at SickKids (TASK)

FULL REPORT

A Micro-costing and Cost Consequence Analysis from a Randomized Controlled Trial Comparing Genome Sequencing to Exome Sequencing for Genetic Diagnosis

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Report No. 2025-01

Date: 2025-04-30

Available at: https://lab.research.sickkids.ca/task/reports-theses/

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Funding and Acknowledgements

Funding was provided by Genome Canada and the Ontario Genomics (OG-186) and the Ontario Ministry of Health. Wendy J. Ungar hold the Canada Research Chair in Economic Evaluation and Technology Assessment in Child Health. Robin Z. Hayeems holds the Canada Research Chair in Genomics and Health Policy. Kym M. Boycott holds the Canada Research Chair in Rare Disease Precision Health. We wish to thank Erin Hsue for assistance with quality control checks.

Executive Summary

Background

Diagnosing rare diseases (RDs) is challenging due to their atypical and diverse symptoms, heterogeneity, and genetic complexity. Genome-wide sequencing, consisting of genome sequencing (GS) and exome sequencing (ES), has emerged as a promising strategy for achieving timely diagnosis of RDs, yet it is not currently routinely available as a clinical test across Canada. Subsequent to a positive funding recommendation by Ontario Health for clinical ES for unexplained developmental disabilities and multiple congenital anomalies, funding was received from Genome Canada and the Ontario Ministry of Health to establish the Genome-wide Sequencing Ontario pilot project. This pilot study, co-led by The Hospital for Sick Children (SickKids), Toronto, Canada, and the Children's Hospital of Eastern Ontario (CHEO), Ottawa, Canada, aimed to evaluate laboratory performance, effectiveness costs, and cost-effectiveness of GWS. The pilot project was designed to furnish additional evidence to inform implementation and a future funding decision regarding GS. The present technical report summarizes the economic component of the pilot study.

Objectives

The objectives of this study were to: (1) estimate the precise cost per trio for both GS and ES using a bottom-up micro-costing approach for a targeted patient population consisting of mostly children with suspected rare genetic conditions and their biological parents and (2) using data from a randomized controlled trial, conduct a cost-consequence analysis (CCA) to estimate the incremental cost of trio GS vs. trio ES per unit improvement in molecular diagnostic yield from an institutional payer perspective.

Methods

The study assessed cost per trio for GS and for ES (Illumina NovaSeq 6000) excluding mark-ups, fees, and charges. The estimation was conducted using a bottom-up micro-costing approach based on the laboratory workflow and the volumes for sequencing-related inputs provided by the Department of Paediatric Laboratory Medicine at SickKids. The total cost was decomposed into seven categories, including reagents, consumables, small and large equipment, shipping and ordering, software, labour and overhead. The analysis was conducted from an institutional payer perspective based on the harmonized diagnostic laboratory practices at SickKids and CHEO. The aggregated cost per trio for GS and ES were determined and the total program costs were estimated for each enrollment year. To

address parameter uncertainty in the model, a probabilistic analysis using Monte Carlo simulations was performed. A CCA was conducted to examine the incremental cost and incremental diagnostic yield of GS vs. ES.

Results

In a cohort of 653 families assessed over a two-year period, 324 trios were randomized to GS, and 329 trios were assigned to ES. The total costs per trio for GS and ES were CAD 4364.02 (95% CI 3984.94, 5013.67) and CAD 2888.79 (95% CI 2567.72, 3492.72) respectively. Reagents were the primary cost component for both strategies, accounting for 61% of the total expenditure for GS and 34% for ES. Software and labour were identified as the second and third highest cost components for GS (15% and 14%, respectively). In contrast, labour and consumables ranked as the second and third most substantial cost components for ES (22% and 18%, respectively). The incremental cost for GS compared to ES was CAD 1475.23, and the diagnostic yields for GS and ES were 32.72% and 35.87%, respectively. The difference between ES and GS diagnostic yield was 0.032 (95% CI: -0.041, 0.104, p-value 0.397).

Conclusions

This study furnished evidence of the cost and cost-effectiveness of trio GS vs. ES using a bottom-up micro-costing approach. GS was associated with higher costs and a similar diagnostic yield for this randomized population with RDs, based on the technical capabilities for sequencing current at the time of the study. The study provides comprehensive costs for future economic evaluations of alternative diagnostic pathways to inform future funding and implementation decisions and impetus for further evaluating variants uniquely detectable by GS.