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

EXECUTIVE SUMMARY

A MICROCOSTING AND COST-CONSEQUENCE ANALYSIS OF GENOMIC TESTING STRATEGIES (INCLUDING TRIOS) IN AUTISM SPECTRUM DISORDER: AN UPDATE

Authors:

Jathishinie Jegathisawaran, MHEcon
Clinical Research Project Coordinator, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada

Kate Tsiplova, MSc
Research Project Manager, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada

Wendy J. Ungar, MSc, PhD
Senior Scientist, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada
Professor, Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

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TASK Technology Assessment at SickKids

Co-investigators:

Christian R. Marshall, PhD
Associate Director, Genome Diagnostics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada
Assistant Professor, Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Dimitri J. Stavropoulos, PhD
Co-Director, Cytogenetics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada
Assistant Professor, Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Sergio L. Pereira, PhD
Research Core Manager, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Bhooma Thiruvahindrapuram, MSc
Facility Manger, Scientific Lead, The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Canada

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Executive Summary

Background

Chromosomal microarray analysis (CMA) is currently the first-tier clinical genetic test for individuals with autism spectrum disorder (ASD). Clinical genome and exome sequencing (CGES) technologies are promising tools for demonstrating genetic causality, due to their higher diagnostic yield compared with CMA for cases presenting with positive phenotypes for ASD. It is not yet clear precisely how the value of CGES technologies can be maximized in a diagnostic pathway or how best to translate these technologies from research to clinical care. An economic evaluation of CGES technologies requires a comprehensive and accurate estimation of all costs involved in the sequencing workflow.

Objectives

The primary objective of this report update is to estimate costs associated with CMA, whole exome sequencing (WES) and whole genome sequencing (WGS) (proband and trio) tests for a targeted patient population consisting of children with ASD from an institutional payer perspective over 5 years. The secondary objective is to compare the incremental costs and diagnostic yields of CMA, WES and WGS in hypothetical clinical testing scenarios in an exploratory cost-consequence analysis.

Methods

Using a bottom-up microcosting approach, the opportunity cost per sample excluding mark-ups, fees and charges for CMA, for WES (on the Illumina HiSeq® 2500 and NextSeq® 550 platforms) and for WGS (probands and trios) on the Illumina HiSeq X™ platform for pediatric patients with ASD were estimated. This was done from an institutional payer perspective based on the diagnostic laboratory practices at The Hospital for Sick Children (SickKids), Canada. The cost per sample was determined for each year of a five-year program. Total program costs to service the ASD pediatric population were also estimated over five years. A probabilistic analysis (PA) was conducted to incorporate parameter uncertainty in the model. Three one-way deterministic sensitivity analyses (DSA) were conducted to examine the effects of changing the inputs for the overhead cost, the total volume of CGES tests in the institution, and the number of primary variants found by CGES tests, while other inputs remained the same. To calculate incremental diagnostic yields for clinical testing scenarios, diagnostic yields were sought from recently published studies reporting diagnostic yields for CMA, WES or WGS (probands and trios) in ASD. A

scenario analysis was also conducted to address a hypothetical, best case scenario of diagnostic yield for WGS-proband. This was varied in each test scenario.

Results

The cost per ASD sample in Year 1 was $1960 (95% CI: 1899, 2020) for WES (HiSeq® 2500), $1981 (95% CI: 1909, 2054) for WES (NextSeq® 550), $3350 (95% CI: 3234, 3467) for WGS-proband (HiSeq X™) and $6556 (95% CI: 6278, 6832) for WGS-trio (HiSeq X™) compared to $825 (95% CI: 789, 859) for CMA. Reagent supply costs accounted for the largest proportion of costs for each type of test. The total institutional program cost to offer CMA for ASD diagnosis over five years was $1.16 million (95% CI: 1.11, 1.21) compared to $2.73 million (95% CI: 2.65, 2.82) for WES (HiSeq®2500), $2.79 million (95% CI: 2.69, 2.89) for WES (NextSeq® 550), $4.68 million (95% CI: 4.52, 4.85) for WGS-proband (HiSeq X™) and $27.78 million (95% CI: 26.59, 28.95) for WGS-trio (HiSeq X™) based on 300 ASD cases per year. The ratio of incremental sample cost to incremental diagnostic yield ranged from $30,154 for CMA plus WES (HiSeq®2500) vs. CMA to $105,349 for WGS-trio (HiSeq X™) vs. CMA plus WES (HiSeq®2500). There is a substantial variation in the ratio depending on the diagnostic yield. For the WGS vs. CMA plus WES scenario, the ratio varied from $34,506 to $105,349. If the WGS diagnostic yield was 42.4%, the cost per additional patient with a positive finding decreased substantially. If WGS-proband replaced CMA, the ratio decreased to $7,630. For WGS-proband vs. CMA plus WES, the incremental sample cost per additional patient with a positive finding was $2,127 for WES- HiSeq® 2500 and $2,049 for WES-NextSeq®550.

Conclusions

This study estimated the cost of trio genome sequencing, in addition to the evaluation of proband through both WES and WGS, using a bottom-up microcosting approach in a clinical paradigm. In contrast, previous study investigated probands only in genome analysis. WGS-trio (HiSeqX™) was the most expensive test, costing almost two times as much as WGS-proband (HiSeq X™), over three times as much as WES on both platforms and almost eight times as much as CMA. The new technology using the NextSeq® 550 platform reduced the cost of WES test only by 1%. Labour and large equipment costs were reduced for the newer platform while the reagent cost increased. Overall, supplies constituted the largest proportion of total cost for all three tests. A cost-consequence analysis revealed a cost of over $30,000 per additional patient with a positive finding if CMA were to be replaced by CMA plus WES or by WGS proband or trio. Additional research is required to assess the impact of CGES on the pathway of

care for children with ASD and to measure ultimate improvements in health outcomes as a result of testing. This study provides comprehensive cost data for use in future economic evaluations of clinical genome and exome sequencing in ASD and allows for a costing model that can be easily adapted to other pediatric patient populations.