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Technology Assessment at SickKids (TASK)

A MICROCOSTING AND COST-CONSEQUENCE ANALYSIS OF GENOMIC TESTING STRATEGIES IN AUTISM SPECTRUM DISORDER

UPDATED

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REPORT HIGHLIGHTS

The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report. Full documents are available for download at:

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Authors

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

Richard M. Zur, PhD
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

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

Daniele Merico, PhD
Facility Manager, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Ted Young, PhD
Laboratory Specialist, Cytogenetics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada

Wilson W.L. Sung, MSc
Bioinformatics Analyst, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Stephen W. Scherer, PhD
Director, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada
Professor of Medicine, Department of Molecular Genetics, University of Toronto, Toronto, Canada

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Introduction

Chromosomal microarray analysis is a first-tier genetic test for children with autism spectrum disorder (ASD) (1, 2). 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 autism spectrum disorder (3, 4). CGES technologies include whole exome sequencing (WES) and whole genome sequencing (WGS). It is not yet clear whether genomic technologies can add value for money invested or how best to translate these technologies from research to clinical care (5, 6). Future economic evaluations of CGES technologies require comprehensive and accurate estimations of all costs involved in the sequencing workflow.

Objectives

The primary objective of this study is to estimate the precise costs associated with CMA, WES and WGS tests using a microcosting approach for a targeted patient population consisting of children with ASD. The secondary objective of the study is to compare the incremental costs and diagnostic yields of CMA, WES and WGS in hypothetical clinical testing scenarios for children with ASD in a cost-consequence analysis.

Key Messages

- The cost per ASD sample was $1655 (95% CI: 1611, 1699) for WES, $2851 (95% CI: 2750, 2956) for WGS on the Illuminia HiSeq X™ platform and $5519 (95% CI: 5244, 5785) for WGS on the Illumina HiSeq® 2500 platform, compared to $744 (95% CI 714, 773) for CMA.

- Estimated five-year program CMA costs were $1.05 million (95% CI: 1.01, 1.09) based on 300 ASD cases. Estimated program costs for WES and WGS tests were also based on 300 ASD cases each. WES program costs were $2.31 million (95% CI: 2.25, 2.37) over five years. Estimated WGS five-year program costs were $7.78 million (95% CI: 7.39, 8.15) for the HiSeq® 2500 platform and $3.98 million (95% CI: 3.84, 4.13) for the HiSeq X™ platform.

- The cost per additional ASD patient with a positive genetic diagnosis was $25459 when substituting CMA alone with CMA+WES. The cost per additional positive genetic diagnosis was $26020 or $58959 when replacing CMA with the WGS HiSeq X™ or WGS HiSeq® 2500 platforms, respectively. The substitution of CMA+WES with WGS resulted in the ratio of incremental cost to incremental diagnostic yield of $28300 using the HiSeq X™ platform and $195056 using the HiSeq® 2500 platform.

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 platform and for WGS on the Illumina HiSeq® 2500 and HiSeq X™ platforms for patients with ASD were estimated from an institutional payer perspective based on the laboratory practices at the Hospital for Sick Children (SickKids), Toronto, Canada. As these tests are currently mainly done in research, a clinical application was simulated for WES and WGS. The cost per sample was determined for each year of a five-year program. Total program costs to service the ASD patient population were also estimated over five years. A probabilistic sensitivity analysis (PSA) 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 associated with clinical scenarios, a review of published studies that reported diagnostic yields for CMA, WES or WGS for patients with ASD was undertaken.

Results

The cost per ASD sample in Year 1 was $1655 (95% CI: 1611, 1699) for WES, $2851 (95% CI: 2750, 2956) for WGS on the HiSeq X™ platform and $5519 (95% CI: 5244, 5785) for WGS on the HiSeq® 2500 platform, compared to $744 (95% CI 714, 773) for CMA (Table 1). The difference in total costs between the HiSeq® 2500 and the HiSeq X™ platforms was largely attributable to the greater cost of reagent supplies and labour for the HiSeq® 2500 platform. The distributions of total cost by cost category for each test are shown in Figure 1.

The total institutional program cost for CMA tests over the five-year period (present value) based on 300 ASD cases per year was $1.05 million (95% CI: 1.01, 1.09). Estimated program costs for WES and WGS tests were also based on 300 ASD cases each. WES program costs were $2.31 million (95% CI: 2.25, 2.37) over five years. Estimated WGS five-year program costs were $7.78 million (95% CI: 7.39, 8.15) for the HiSeq® 2500 platform and $3.98 million (95% CI: 3.84, 4.13) for the HiSeq X™ platform. Due to economies of scale, the sample and program costs of WES decreased by 15% when the number of WES tests for all indications increased from 500 to 1000. Increasing the number of tests for all indications from 500 to 1000 reduced the sample and

program cost of WGS by 4% for the HiSeq® 2500 platform and by 13% for the HiSeq X™ platform. The relatively small cost reduction for WGS HiSeq® 2500 platform was due the high cost of reagent supplies which would increase when scaling up test volume.

Based on a literature review, the diagnostic yield for ASD used in the cost consequence analysis was 9.3% for CMA and 15.8% for a combination of CMA + WES, where all patients would receive both tests. A hypothetical diagnostic yield for WGS was calculated to be 17.8%. The cost per additional patient with a positive genetic finding was $25459 when substituting CMA alone with CMA+WES (Table 2). The cost per additional patient with a positive genetic finding was $58959 or $26020 when replacing CMA with the WGS HiSeq® 2500 or with HiSeq X™ platforms, respectively. The substitution of CMA+WES with WGS alone resulted in an incremental cost of $28300 per additional patient with a positive genetic finding for the HiSeq X™ platform and $195056 for the HiSeq® 2500 platform.

Discussion

This study is the first to estimate the cost of clinical exome and genome sequencing using a bottom-up microcosting approach in a clinical paradigm. The WGS using older technology (HiSeq® 2500) was the most expensive test, costing almost three times as much as WES and seven times as much as CMA. The new technology using the HiSeq X™ platform reduced the cost of WGS test by 48%. Labour costs were reduced for HiSeq X™ due to improved automation and streamlining of sample processing. Overall, supplies, followed by equipment and labour, constituted the largest proportion of total cost for all three tests.

In the present analysis, alternative scenarios were presented as complete substitutions, e.g. combination testing with CMA plus WES for all patients replacing CMA alone, or WGS replacing CMA. This approach would be very costly, as the cost-consequence analysis revealed an incremental cost of over $25000 for every additional patient with a pathologic variant beyond expected CMA results if CMA were to be wholly replaced by CMA+WES or by WGS. In reality, the precise sequence and type of serial testing will vary with the patient population, the anticipated diagnostic yields as well as the cost of testing. It is also likely to vary, at least in the short-term, between clinical practitioners. Practice variation in genetic test ordering between clinicians makes it difficult to determine the potential for savings through the avoidance of older generation genetic

tests. It is hoped that as CGES becomes more established in clinical practice, test ordering protocols that prevent the ordering of superfluous tests will be implemented.

The estimated cost per sample for CMA was comparable to published reports. Trakadis and Shevell reported a CMA cost of approximately $682 (CAD, 2010) for children with global development delay (7). Woodworth *et al.* estimated the cost of CMA for diagnosis of idiopathic learning disability using data from four participating genetic centers in United Kingdom to be 442 £ ($924 CAD) (8) using the average 2006 UK Pound/CAD exchange rate of 2.09 (9). Regier *et al.* reported a CMA cost of $710 (2007/2008 CAD) for genetic causes of intellectual disability in children (10).

Published estimates for WES or WGS costs are limited (11, 12). Wright *et al.* noted that WGS costs approximately 6000 £ ($9660 CAD, 2013) and WES approximately 200-500 £ ($322-805 CAD, 2013) (13). Neither study provided a breakdown of included items or the platform used. Monroe *et al.* examined the use of WES in patients with intellectual disability, a group that may be subjected to numerous genetic and metabolic tests in search of a diagnosis (14) They estimated the cost of trio-WES at $3972 USD ($4409 CAD, 2014) (9). That estimate included the costs of patient registration and blood draw, DNA isolation, sample preparation, exome enrichment, sequencing on an Illumina HiSeq® 2500, interpretation, reporting of results, data storage and infrastructure. Monroe *et al.* also calculated the amount that could potentially be saved by replacing the standard genetic and metabolic testing in patients with intellectual disability with WES as a first tier test. On average, WES was found to save $3547 USD ($3937 CAD) per patient receiving a diagnosis and $1727 USD ($1917 CAD) for patients not receiving a diagnosis using WES.

The study has several strengths. All stages and costs involved in the workflow of CMA, WGS and WES were accounted for using the microcosting approach generating the first fully comprehensive per sample and program cost estimates of CGES. The provision of estimates for two different WGS platforms increased the generalizability of the findings and its value for decision-makers. Although the estimates in this report are for an ASD patient population, the microcosting model was constructed to be flexible and easily adapted to other patient populations by simply varying the number of primary variants and the volume of testing in the institution. There are several limitations to the study. WES has only very recently been implemented in clinical use and WGS is currently a purely research application. The WGS costs were calculated as expected costs in a clinical setting based on WES microcosting and expert opinion, rather than by costing the research application or

by applying charges from an external service provider. Thus the actual costs of WGS once clinical testing is introduced may diverge from the predicted estimates. The cost estimates did not include training of technical and lab personnel, implementation costs, genetic counseling or health care provider services. These could be considerable, especially in early generations of a technology experiencing rapid evolution.

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. It is essential that programs of health services and policy research that perform such studies are executed in tandem with translation of CGES into clinical practices to generate evidence to inform institutional and provincial health policy decision-makers (15).

Table 1. Estimated total annual cost per ASD sample for CMA, WES and WGS in Year 1

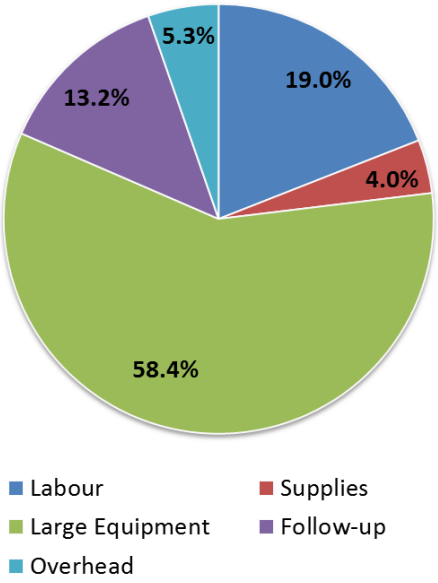
Cost Category	CMA (95% CI)	WES (95% CI)	WGS, HiSeq® 2500 (95% CI)	WGS, HiSeq X™ (95% CI)
Labour	141.6 (132.2, 151)	318.4 (294.6, 342.6)	518.4 (469.4, 568.7)	250.5 (225.9, 274.5)
Large Equipment	30 (28.2, 31.9)	385.6 (369.9, 400.9)	385.6 (370, 401.3)	583.8 (550, 617.3)
Small Equipment	N/A	8.9 (8.6, 9.2)	8.9 (8.6, 9.2)	8.9 (8.6, 9.2)
Supplies	434.6 (409.1, 459.3)	657.7 (633.3, 681.7)	4066.3 (3803.2, 4324.7)	1380.1 (1297.6, 1464.6)
Follow-up	98 (89, 107.4)	112 (101.1, 123.1)	178.6 (158.2, 200.5)	178.8 (158.4, 200.9)
Bioinformatics	N/A	6.7 (6, 7.5)	123.2 (108.1, 138.7)	207.5 (189.9, 225)
Overhead	39.5 (37.3, 41.7)	165.5 (158.9, 172.1)	238.3 (225.8, 251)	241.7 (231.2, 252.1)
Total	**743.7 (714.1, 773)**	**1654.8 (1611, 1698.5)**	**5519.3 (5243.7, 5785.4)**	**2851.2 (2750, 2955.5)**

Estimates are given in 2015 Canadian dollars (CAD). Confidence intervals (CI) are based on 10000 Monte Carlo replications. The results are based on reference levels for overhead costs of 23%; 3948 CMA tests done for all indications per year; 500 WES/WGS total tests done for all indications per year; and two primary variants found per WES/WGS test.

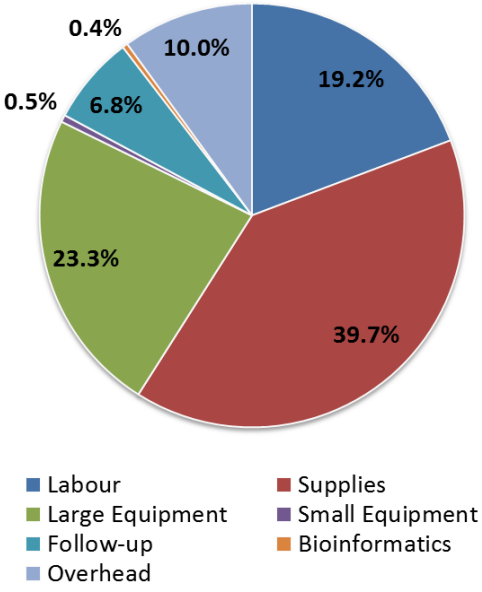
Abbreviations: ASD, Autism spectrum disorder; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing

Figure 1. Proportion of total annual cost per ASD test by cost category for CMA, WES, WGS (HiSeq® 2500) and WGS (HiSeq X™), Year 1.

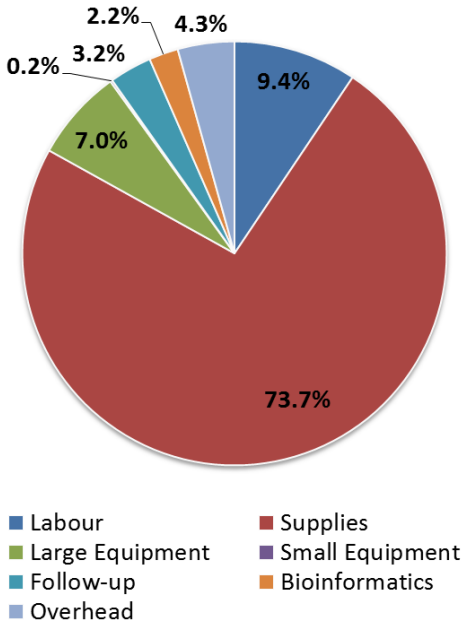
(a) CMA ($744)



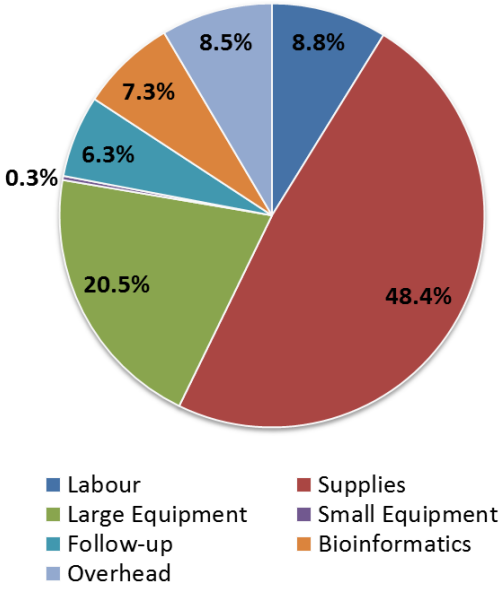
(b) WES ($1655)



(c) WGS (HiSeq® 2500) ($5519)



(d) WGS (HiSeq X™) ($2851)



Estimates are given in 2015 Canadian dollars (CAD).
Abbreviations: ASD, Autism spectrum disorder; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing

Table 2. Estimated total annual incremental cost per ASD sample, estimated incremental ASD diagnostic yield and estimated incremental cost per additional ASD patient with a positive finding, Year 1

Scenario	Incremental sample cost, CAD (95% CI)	Incremental diagnostic yield	Incremental ratio
1. CMA+WES vs. CMA	1654.8 (1611, 1698.5)	0.065	25458.5
2. WGS vs. CMA			
2.1 WGS (HiSeq® 2500) vs. CMA	4775.7 (4499.2, 5042.6)	0.081	58959.3
2.2 WGS (HiSeq X™) vs. CMA	2107.6 (2002.9, 2215.2)	0.081	26019.8
3. WGS vs. CMA+WES			
3.1. WGS (HiSeq® 2500) vs. CMA+WES	3120.9 (2841.6, 3392.1)	0.016	195056.2
3.2. WGS (HiSeq X™) vs. CMA+WES	452.8 (339.2, 570.2)	0.016	28300.0

Estimates are given in 2015 Canadian dollars (CAD). Confidence intervals (CI) for incremental cost are based on 10000 Monte Carlo replications.

Abbreviations: ASD, Autism spectrum disorder; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing

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