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

SUPPLEMENT

A MICROCOSTING AND COST-CONSEQUENCE ANALYSIS OF GENOMIC TESTING STRATEGIES (INCLUDING TRIOS) IN CHILDREN WITH CONGENITAL ANOMALIES AND DEVELOPMENTAL DELAY: 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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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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Table of Contents

1. Background and assumptions

In this supplemental analysis, sample and program costs and the incremental cost to incremental diagnostic yield ratios were calculated for children with congenital anomalies (CA) and developmental delay (DD). Developmental delay may include autism spectrum disorder (ASD). In contrast to a target population approach used in the report, this analysis assumes a more heterogeneous group of children in a centralized clinic approach. These patients may present with a developmental delay phenotype but have not yet received a clinical diagnosis.

The model assumptions that were made to determine cost per CA/DD sample and 5-year program costs for CMA, whole exome sequencing (WES) and whole genome sequencing (WGS) are listed in Table 1. For CMA, the average total number of tests done per year in the institution for all indications was 3948, based on the 2013/14 fiscal year. These figures have not changed for 2018 or for this update. Of these, 79.6% of all CMA tests were conducted for patients with DD (Stavropoulos, DJ, personal communication). It was assumed that the maximum number of WES/WGS (probands) tests done per year in the institution for all indications was 1000 and for trios, it was assumed to be 3000. Of all of these tests, 79.6% (probands – 796; trios – 2388) would be conducted for DD.

The diagnostic yields of WGS and CMA for children with CA and DD were obtained from Stavropoulos *et al.* (2016) [1]. In the study, 100 paediatric patients (probands) were offered CMA and WGS. The diagnostic yield was estimated to be 8% for CMA only and 34% for WGS. No study with a similar population that measured the diagnostic yield of CMA combined with WES was found for the analysis in the previous version of the supplement. There are no updates in the literature for the current supplement update. Therefore, the only clinical scenario considered was WGS vs. CMA. Bowling *et al.* (2017) [2] investigated genomic data on children with intellectual disability (ID) and/or DD using WES and WGS. The groups included in the analyses were probands, duos and trios. Of the 309 trios (from 284 families), 29.1% were found to have positive or likely positive variants. Diagnostic yields of duos and probands were 19.0% and 15.0%, respectively. Trio testing provides the advantage of identifying *de novo* variants at a much faster rate. This is in addition to the ease of identifying VUSs which would otherwise be more challenging in proband only analyses. There may be other downstream consequences that could impact the cost efficiency either by increasing it or minimizing it.

Table 1. Inputs for analysis for children with CA and DD

	CMA	WES HiSeq® 2500	WES NextSeq® 550	WGS-proband HiSeq X™	WGS-Trio HiSeq X™
Total tests performed on large or small equipment per year (including condition of interest)	3948	1000	1000	1000	3000
Proportion of all tests for indicated condition	79.62%	79.62%	79.62%	79.62%	79.62%
Number of disease tests performed per year	3143	796	796	796	2388
Number of primary variants per test (WES, WGS)	N/A	2	2	2	2
Diagnostic yield of test	0.08	N/A	N/A	0.34	0.36

Abbreviations: CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing.

2. Results

2.1 Costs for children with CA and DD

The mean total costs per sample for CMA, WES (HiSeq® 2500), WES (NextSeq® 550), WGS-proband (HiSeq X™) and WGS-trio (HiSeq X™) for Year 1 of a 5-year testing service are shown in Table 2. The annual cost of CMA per CA/DD sample was $824.50 (95% CI: 789.00, 858.90). The annual cost per CA/DD sample of WES (HiSeq® 2500) was 1718.80 (95% CI: 1660.40, 1775.40), and on NextSeq® 550 platform it was $1904.90 (95% CI: 1834.00, 1976.10). The annual cost per CA/DD sample of WGS-proband on HiSeq X™ was deemed to be $2988.10 (95% CI: 2878.00, 3101.40) while WGS-trio conducted on HiSeq X™ was $6435.20 (95% CI: 6149.60, 6712.00).

Table 2. Estimated annual cost per CA/DD sample for CMA, WES and WGS.

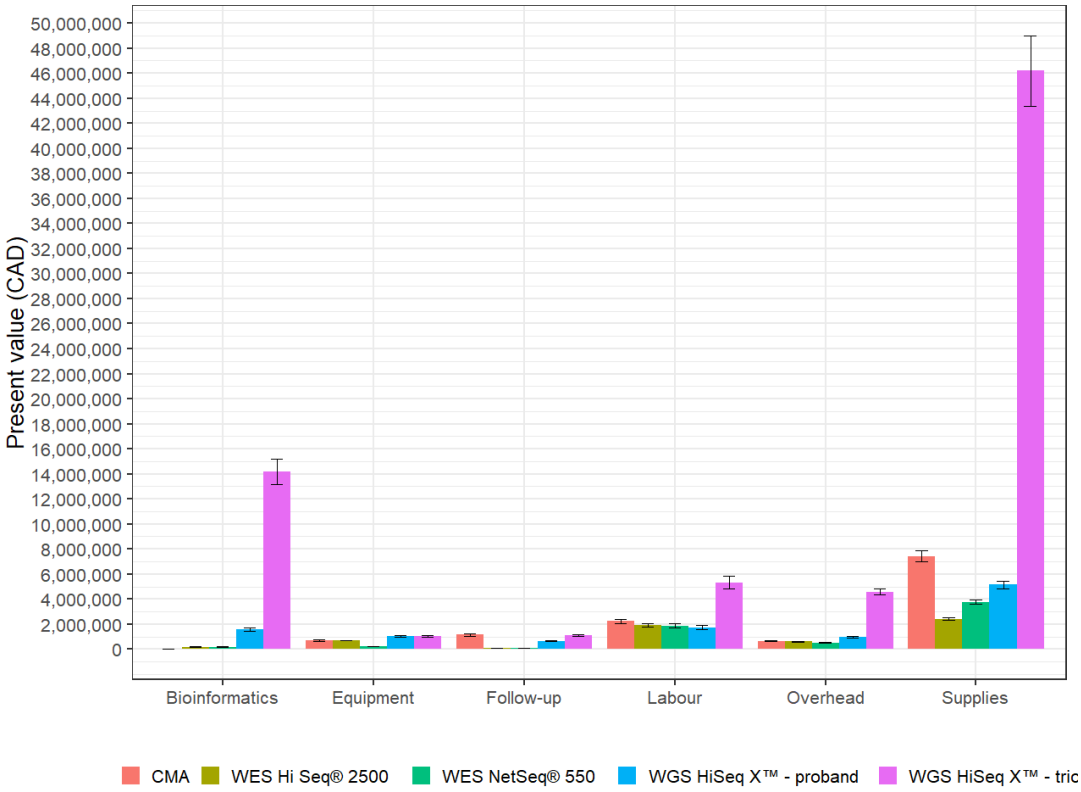
Cost Category	CMA (95% CI)	WES, HiSeq® 2500 (95% CI)	WES, NextSeq® 550 (95% CI)	WGS- proband, HiSeq X™ (95% CI)	WGS- trio, HiSeq X™ (95% CI)
Labour	151.3 (139.3, 163.5)	506.3 (465.7, 545.9)	499.8 (457.8, 543)	464.7 (417.4, 514.2)	473.7 (430.9, 519.7)
Large Equipment	50.1 (47.1, 53.1)	192.8 (185, 200.4)	57.5 (54.5, 60.6)	291.8 (274.9, 308.5)	97.3 (91.7, 103)
Small Equipment	N/A	4.40 (4.2, 4.5)	4.4 (4.2, 4.5)	4.40 (4.2, 4.5)	1.50 (1.4, 1.5)
Supplies	501.2 (470.3, 531.1)	643.2 (617.9, 668.2)	1002.7 (955.9, 1048.3)	1367.6 (1284.5, 1449.5)	4100.2 (3847.8, 4348.9)
Follow-up	76.9 (69.1, 84.8)	155.4 (141.8, 169.8)	155.3 (141.4, 169.6)	177 (162.6, 191.9)	96.3 (89.5, 103)
Bioinformatics	N/A	49.1 (45.8, 52.4)	49 (45.8, 52.3)	419.4 (390, 448.9)	1258.1 (1170.3, 1345.9)
Overhead	44.9 (42.1, 47.7)	167.8 (158.5, 176.9)	136.2 (126.8, 145.9)	263.2 (250.3, 276.3)	408.2 (386.3, 430.2)
Total	824.5 (789, 858.9)	1718.8 (1660.4, 1775.4)	1904.9 (1834, 1976.1)	2988.1 (2878, 3101.4)	6435.2 (6149.6, 6712)

Estimates are given in 2018 Canadian dollars (CAD) for year 1 of a 5-year program. Confidence intervals (CI) are based on 10,000 Monte Carlo replications. Results are based on overhead costs of 22.3%; 3948 CMA, 1000 WES, 1000 WGS-proband and 3000 WGS-trio tests for all indications per year; and two primary variants found per WES/WGS test.

Abbreviations: CA, Congenital anomalies; DD, Developmental delay; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing.

The total program cost to offer CMA for CA/DD diagnosis over five years was $12.2 million (95% CI: 11.6, 12.7). The five-year program costs of CGES for CA/DD were $6.4 million (95% CI: 6.2, 6.6) for WES on HiSeq® 2500 and $7.1 million (95% CI: 6.9, 7.4) on NextSeq®550 platform. For WGS-proband on HiSeq X™ the costs were $11.1 million (95% CI: 10.7, 11.6) and for WGS-trio on HiSeq X™ it was $72.4 million (95% CI: 69.2, 75.6). Figure 1 shows the present value of program costs for each major cost category and for each test.

Figure 1. Present value of CA/DD program costs over five years for CMA, WES and WGS.



Estimates are given in 2018 Canadian dollars (CAD). Confidence bands are based on 10,000 Monte Carlo replications. Program costs are based on 3143 CMA tests, 796 WES/WGS-proband tests and 2388 WGS-trio tests done annually at the institution.

Abbreviations: CA, Congenital anomalies; DD, Developmental delay; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing

2.2 Cost-Consequence Analysis for children with CA or DD

For WGS-proband (HiSeq X™) vs. CMA, the incremental cost to diagnostic yield ratio was $8321.54 in Year 1 of the five-year program. This is less than 50% in comparison to the pair of WGS-trio vs. CMA on the same platform. With an incremental difference of 2% in the diagnostic yield of a trio, the incremental ratio for this pair was found to be $20,038.57 (Table 3).

Table 3. Estimated total annual incremental cost per CA/DD sample, estimated incremental diagnostic yield and estimated incremental cost per additional patient with a positive finding, Year 1

Scenario	**Incremental sample cost (CAD) (95% CI)**	**Incremental diagnostic yield (diagnosis rate)**	**Incremental ratio (CAD/diagnosis rate)**
1. WGS vs. CMA			
1.1 WGS-proband (HiSeq X™) vs. CMA	2163.60 (2048.70, 2279.90)	0.26	8321.54
1.2 WGS-trio (HiSeq X™) vs. CMA	5610.80 (5324.50, 5891.30)	0.28	20,038.57

Estimates are given in 2018 Canadian dollars (CAD). Confidence intervals (CI) for incremental cost are based on 10,000 Monte Carlo replications.

Abbreviations: CA, Congenital anomalies; DD, Developmental delay; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing.

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