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

SUPPLEMENT

Updated

A MICROCOSTING AND COST-CONSEQUENCE ANALYSIS OF GENOMIC TESTING STRATEGIES IN CHILDREN WITH CONGENITAL ANOMALIES AND DEVELOPMENTAL DELAY

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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 DD/CA sample and 5-year program costs for CMA, WES and 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. Of these, 79.6% of all CMA tests were conducted for patients with developmental delay (Stavropoulos, DJ, personal communication). It was assumed that the maximum number of WES/WGS tests done per year in the institution for all indications was 1000 and that 79.6% (796) of these tests would be conducted for developmental delay.

The diagnostic yields of WGS and CMA for children with congenital anomalies and developmental delay were obtained from Stavropoulos *et al.* (2016) (1). In the study, 100 paediatric patients 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. Therefore, the only clinical scenario considered was WGS vs. CMA.

Table 1. Inputs for analysis for children with congenital malformations and developmental delay

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

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

Summary of costs for children with developmental delay or congenital anomalies

The mean total costs per sample for CMA, WES, WGS (HiSeq® 2500) and WGS (HiSeq X™) for Year 1 of a 5-year testing service are shown in Table 2. The annual cost of CMA per DD/CA sample was $744 (95% CI: 715, 773). The annual cost per DD/CA sample of WES was $1412 (95% CI: 1372, 1452). The annual cost per DD/CA sample of WGS was $5275 (95% CI: 5007, 5538) conducted on HiSeq® 2500 and $2488 (95% CI: 2395, 2580) conducted on HiSeq X™.

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

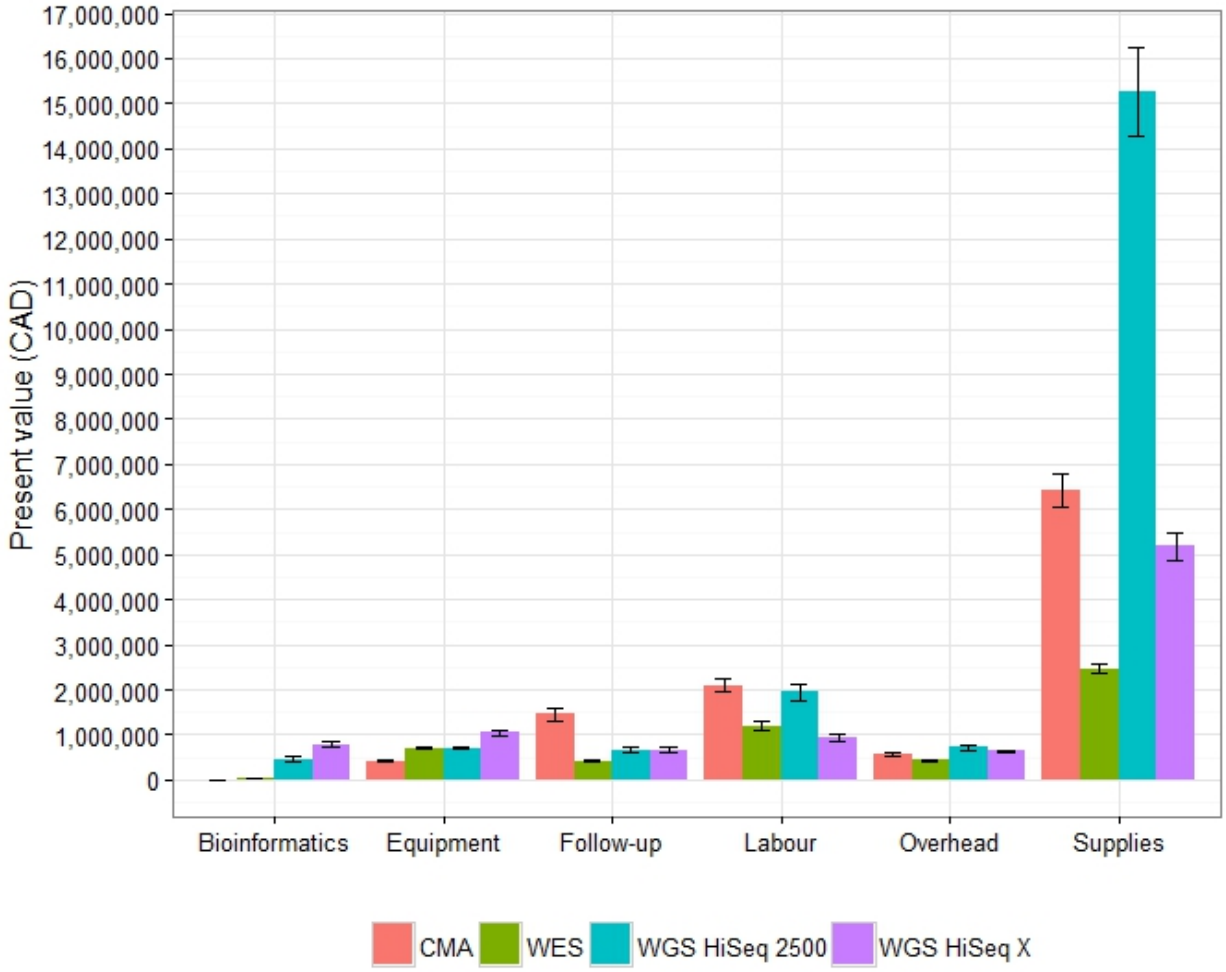
Cost Category	**CMA (95% CI)**	**WES (95% CI)**	**WGS, HiSeq® 2500 (95% CI)**	**WGS, HiSeq X™™ (95% CI)**
Labour	141.5 (132.4, 150.8)	318.3 (294.2, 342)	518.1 (467.9, 570)	251 (226.2, 275.2)
Large Equipment	30 (28.1, 31.9)	192.8 (185.2, 200.6)	192.8 (184.8, 200.3)	292 (275.2, 309)
Small Equipment	434.4 (409.7, 460.3)	4.4 (4.3, 4.6)	4.4 (4.3, 4.6)	4.4 (4.3, 4.6)
Supplies	98.1 (89, 107.6)	657.7 (634, 681.5)	4065.3 (3806, 4322.5)	1381 (1298, 1460.6)
Follow-up	141.5 (132.4, 150.8)	112.2 (103.7, 120.8)	178.6 (163.7, 194.3)	178.7 (163.6, 195)
Bioinformatics	N/A	6.7 (6, 7.5)	123.4 (108, 139)	207.5 (190.1, 225.4)
Overhead	39.5 (37.3, 41.6)	120.1 (114.3, 125.9)	192.9 (180.6, 205.3)	173.6 (165.7, 181.6)
Total	743.6 (714.7, 772.9)	1412.2 (1372.3, 1452.2)	5275.4 (5007.2, 5538.1)	2488.3 (2394.9, 2580.1)

Estimates are given in 2015 Canadian dollars (CAD) for year 1 of a 5-year program. Confidence intervals (CI) are based on 10000 Monte Carlo replications. Results are based on overhead costs of 23%; 3948 CMA, 1000 WES and 1000 WGS tests for all indications per year; and two primary variants found per WES/WGS test.

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

The total program cost to offer CMA for DD/CA diagnosis over five years was $11.0 million (95% CI: 10.6, 11.4). The five-year program costs of CGES for DD/CA were $5.26 million (95% CI: 5.11, 5.41) for WES, $19.8 million (95% CI: 18.8, 20.8) for WGS on HiSeq® 2500 and $9.28 million (95% CI: 8.93, 9.62) for WGS on HiSeq X™. Figure 1 shows the present value of program costs for each major cost category and for each test.

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



Estimates are given in 2015 Canadian dollars (CAD). Confidence bands are based on 10000 Monte Carlo replications. Program costs are based on 3143 CMA tests and 796 WES/WGS tests done annually at the institution.
Abbreviations: DD, Developmental delay; CA, Congenital anomalies; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing

Cost-Consequence Analysis for children with MCA or DD

For WGS (HiSeq® 2500) vs. CMA, the incremental cost to diagnostic yield ratio was $17430 in Year 1 of the five-year program. The incremental cost per additional patient with a positive finding was reduced by more than half if WGS is performed on the HiSeq X™ platform, to $6710 (Table 3).

Table 3. Estimated total annual incremental cost per DD/CA 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)
2. WGS vs. CMA			
2.1 WGS (HiSeq® 2500) vs. CMA	4531.8 (4260.6, 4796.8)	0.26	17430.0
2.2 WGS (HiSeq X™) vs. CMA	1744.8 (1646.7, 1841.4)	0.26	6710.4

Estimates are given in 2015 Canadian dollars (CAD). Confidence intervals (CI) for incremental cost are based on 10000 Monte Carlo replications.
Abbreviations: DD, Developmental delay; CA, Congenital anomalies; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing.

Bibliography

1. Stavropoulos DJ, Merico D, Jobling R, Bowdin S, Monfared N, Thiruvahindrapuram B, et al. Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. Npj Genomic Medicine. 2016;1(15012).