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Technology Assessment at SickKids (TASK)

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

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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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Introduction

Chromosomal microarray analysis (CMA) 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 ASD [3, 4]. CGES technologies include whole exome sequencing (WES) and whole genome sequencing (WGS). Traditionally, WGS has been conducted with probands only, with follow-up testing extended to include the two biological parents in addition to the probands. However, the use of trio testing is on the rise for both WES and WGS. Utilization of trio sequencing method enhances the speed and likelihood of accurate diagnosis by decreasing the number of candidate variants [5]. Diagnostic rate can also be improved and the chance of missing a *de novo* variant is reduced through cross-checking of the gene/phenotype database by geneticists/ genetic counsellors [6]. It is not yet clear whether CGES technologies can add value for money invested or how best to translate these technologies from research to clinical care [7, 8]. Economic evaluations of CGES technologies require comprehensive and accurate estimations of all costs involved in the sequencing workflow.

Key Messages

- 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.

- Estimated five-year program CMA costs were $1.16 million (95% CI: 1.11, 1.21) 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 $2.73 million (95% CI: 2.65, 2.82) on the HiSeq®2500 platform and $2.79 million (95% CI: 2.69, 2.89) on the NextSeq® 550 platform over five years. Estimated WGS five-year program costs were $4.68 million (95% CI: 4.52, 4.85) for the probands and $27.78 million (95% CI: 26.59, 28.95) for trios, both on the HiSeq X™ platform.

- The cost per additional ASD patient with a positive genetic diagnosis was $30,154 when substituting CMA alone with CMA+WES (HiSeq 2500®). On the NextSeq ® 550 platform, it was $30,471. When comparing WGS-proband to CMA alone, incremental cost to diagnostic yield ratio was $31,260. For the trio analysis it was $56,860. The incremental cost was $35,810 for the WGS-proband vs. CMA+WES on the HiSeq® 2500 platform and $34,506 on the NextSeq® 550 platform. When the same two scenarios were conducted with trio, the incremental costs for every additional patient with a positive finding were $105,349 and $104,773, for each platform respectively.

Objectives

The primary objective of this report update is to estimate the precise costs associated with CMA, WES and WGS (proband and trio) 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 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 patients with ASD were estimated from an institutional payer perspective based on the diagnostic laboratory practices at The Hospital for Sick Children (SickKids), Toronto, Canada. While WGS is currently conducted in the research context, WES is in transition from research into clinical practice. 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 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 associated with clinical scenarios, a review of published studies that reported diagnostic yields for CMA, WES or WGS (proband and trio) for patients with ASD was undertaken.

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 (Table 1). Reagent supply costs accounted for the largest proportion of costs for each type of test. 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 $1.16 million (95% CI: 1.11, 1.21). Estimated program costs for WES (both platforms) and WGS (proband and trio) tests were also based on 300 ASD cases each. WES program costs were $2.73 million (95% CI: 2.65, 2.82) on the HiSeq®2500 platform and $2.79 million (95% CI: 2.69, 2.89) on the NextSeq® 550 platform over five years. Estimated WGS five-year program costs were $4.68 million (95% CI: 4.52, 4.85) for the probands and $27.78 million (95% CI: 26.59, 28.95) for trios, both on the HiSeq X™ platform (Figure 2). Due to economies of scale, the sample costs of WES decreased by 13.3% when the number of WES tests for all indications increased from 500 to 1000 on HiSeq® 2500. In contrast, the decrease of the sample costs was a minimal, 0.5%, on NextSeq® 550 platform. This may be attributed to the increased cost of sequencing reagents needed for the platform and the relatively low price of the platform. Increasing the number of tests for all indications from 500 to 1000 reduced the sample cost of WGS-proband by 12% on the HiSeq X™ platform. The sample costs of WGS-trio on the same platform declined by 1.6% when the number of tests for all indications were increased from 1500 to 3000. The relatively minimal cost reduction for trios was due to the three factor increase in the use and cost of supplies and computation for the increased number of samples.

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-proband was calculated to be 17.38%. Based on expert opinion, the increase in the diagnostic yield for trio was deemed to be 2% and therefore, the yield for trio in the cost-consequence analysis was 19.38%. The cost per additional patient with a positive genetic finding was $30,154 when substituting CMA alone with CMA+WES (HiSeq 2500®) (Table 2). On the NextSeq ® 550 platform, this figure changed to $30,471. When comparing WGS-proband to CMA alone, incremental cost

to diagnostic yield ratio was $31,260. When WGS-trio was substituted for the WGS-proband, the incremental ratio was $56,860. The incremental cost was $35,810 for the WGS-proband vs. CMA+WES on the HiSeq® 2500 platform and it changed to $34,506 for the NextSeq® 550 platform. When the same two scenarios were conducted with trio instead of proband, the incremental costs for every additional patient with a positive finding were $105,349 and $104,773, for each platform respectively.

Discussion

In this study, the sample and program costs of proband on CMA, WES and WGS tests were evaluated in addition to trio on WGS for children with ASD. 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. Per person cost of a trio however was found to be less expensive compared to proband test by a factor of 1.53. The costs of WES for two different platforms, NextSeq® 550 and HiSeq® 2500, were nearly the same.

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, WGS (proband or trio) replacing CMA or WGS (proband or trio) replacing CMA plus WES. Either of the three approaches would be very costly, as the cost-consequence analysis revealed an incremental cost of over $30,000 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 (proband or trio). If WGS-trio replaced CMA plus WES, the incremental ratio was greater than $100,000 per diagnostic rate. 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 [9]. 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) [10] using the average 2006 UK Pound/CAD exchange rate of 2.09 [11]. Regier *et al.* reported a CMA cost of $710 CAD (2007/2008) for genetic causes of intellectual disability in children [12].

Published estimates for WES or WGS costs are currently limited [13, 14]. Wright *et al.* noted that WGS costs approximately £6000 ($9660 CAD, 2013) and WES approximately £200-500 ($322-805 CAD, 2013) [15]. 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 [16]. They estimated the cost of trio-WES at $3972 USD ($4409 CAD, 2014) [11]. 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. Stark *et al.* (2017) analyzed the cost-effectiveness of singleton WES by comparing it to standard of care in infants with monogenic disorders. If WES was performed as a last resort (after exhaustion of standard diagnostic care options), the incremental cost per standard diagnosis was found to be $8,112 AUD ($7605 CAD, 2015). If, on the other hand, WES was a first-line test (replacing all other diagnostic options), the result was savings in cost of $2,182 AUD ($2045 CAD, 2015). In the first scenario, all appointments, pathology tests, imaging, genetic testing and other costs related to standard of care were included. In the second scenario, two appointments and SNP microarray costs were included for the incremental analysis. Tan *et al*. (2017) conducted similar research in children with suspected monogenic conditions who were non-diagnostic of SNP microarray. Costs captured in their analysis included initial visit to tertiary services for diagnostic purposes, first clinical genetics assessment, enrollment and WES report, among others. Compared to standard diagnostic care without WES, care with WES generated an incremental cost per additional diagnosis of $5760 AUD ($5400 CAD, 2015). In the alternate scenario where WES was performed after the first clinical genetics consultation, there was a savings of $5461 AUD ($5120 CAD, 2015) per additional diagnosis. This cost savings increased to $9020 AUD ($8457 CAD, 2015) if the WES was at initial tertiary presentation.

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 both proband and trio on the WGS platform provided information for decision makers on the value that trio analysis can add in comparison to proband analysis if WGS were to be implemented as standard clinical practice. 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. In Canada, 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. In the case of trio analysis of WGS, the decreased wait time of 2-3 weeks on Sanger sequencing was not incorporated in the economic models. Other downstream consequences, if modelled would provide further insight into the possible benefits and/or disadvantages of trio analysis in comparison to proband testing.

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 [17].

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

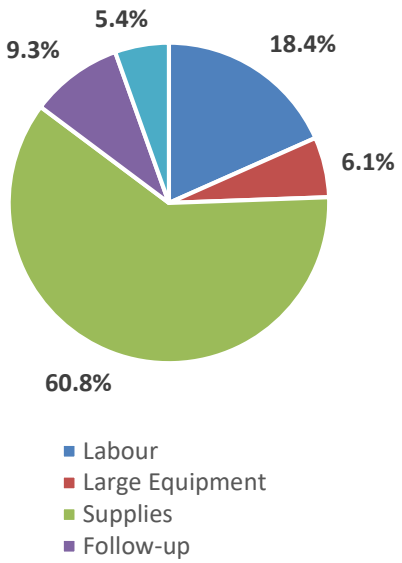
Cost Category	CMA (95% CI)	WES-Hi Seq® 2500 (95% CI)	WES-Hi Seq® 550 (95% CI)	WGS-proband HiSeq X™ (95% CI)	WGS-trio HiSeq X™ (95% CI)
Labour	151.3	506.3	499.8	464.7	473.7
	(139.3, 163.5)	(465.1, 546.7)	(457.8, 544.2)	(417.2, 515.3)	(430.6, 520.5)
Large Equipment	50.1	385.5	115.1	583.6	194.6
	(47.1, 53.1)	(370, 400.9)	(109, 121.2)	(549.8, 617)	(183.4, 206.1)
Small Equipment	N/A	8.8	8.8	8.8	2.9
	N/A	(8.5, 9.1)	(8.5, 9.1)	(8.5, 9.1)	(2.8, 3)
Supplies	501.2	643.2	1002.7	1367.5	4099.9
	(470.3, 531.1)	(617.9, 668.2)	(955.9, 1048.4)	(1284.5, 1448.9)	(3847.7, 4348.8)
Follow-up	76.9	155.4	155.3	177	96.2
	(69.1, 84.8)	(138.9, 173)	(138.7, 172.4)	(159, 195.4)	(87.8, 104.8)
Bioinformatics	N/A	49.1	49	419.4	1258.3
	N/A	(45.8, 52.3)	(45.9, 52.3)	(390.6, 449.1)	(1172.8, 1346.7)
Overhead	44.9	211.8	150	329.3	430.3
	(42.1, 47.7)	(201.9, 221.5)	(140.5, 160.1)	(314.5, 344.1)	(408.5, 452.4)
Total	**825**	**1960**	**1981**	**3350**	**6556**
	(789, 859)	**(1899, 2020)**	**(1909, 2054)**	**(3234, 3467)**	**(6278, 6832)**

Estimates are given in 2018 Canadian dollars (CAD). Confidence intervals (CI) are based on 10,000 Monte Carlo replications. The results are based on reference levels for overhead costs of 22.3%; 3948 CMA tests done for all indications per year; 500 WES/WGS-proband total tests done for all indications per year; 1500 total tests done for all indications per year and two primary variants found in each CGES test.

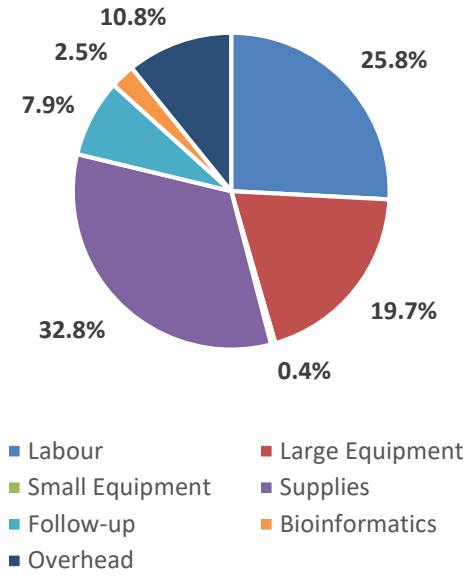
Abbreviations: ASD, Autism spectrum disorder; CMA, Chromosomal microarray analysis; WES, Whole exome sequencing; WGS, Whole genome sequencing

Figure 1. Proportion of total annual cost per ASD test by cost category for CMA (a), WES (HiSeq ® 2500) (b), WES (NetSeq® 550) (c), WGS-proband (HiSeq® HiSeq X™) (d), WGS-trio (HiSeq X™) (e), Year 1.

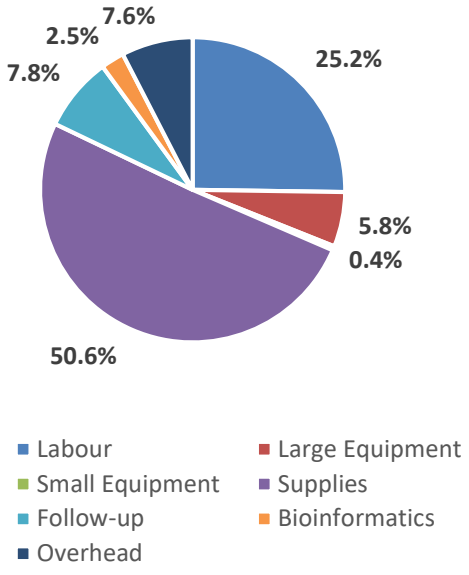
(a) CMA ($825)



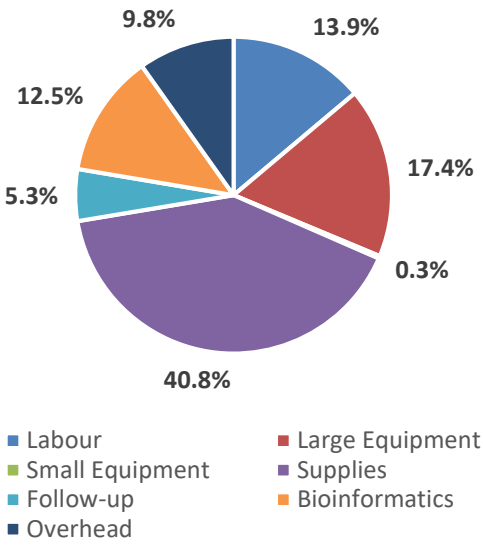
(b) WES- HiSeq ® 2500 ($1960)



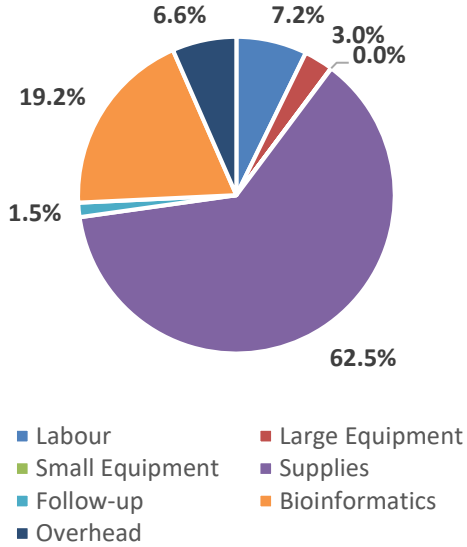
(c) WES (NetSeq® 550) ($1981)



(d) WGS (HiSeq X™ proband) ($3350)



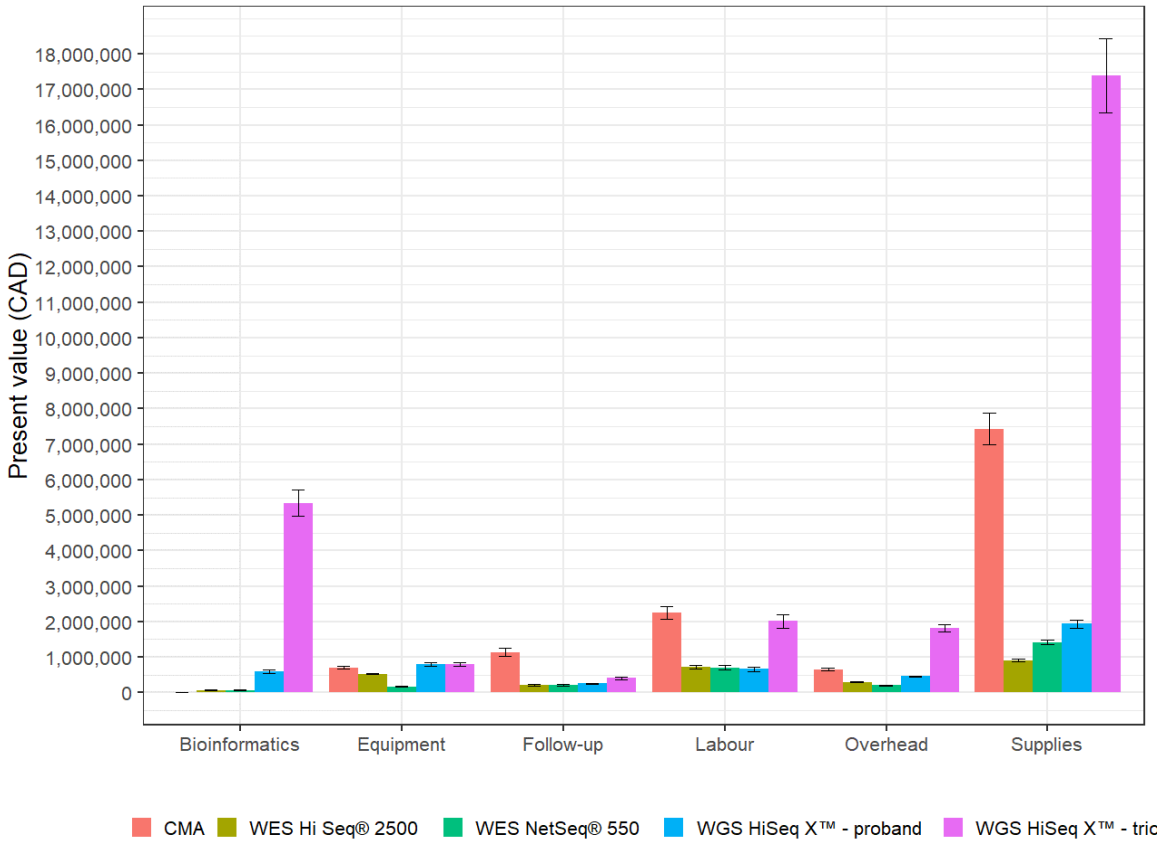
(e) WGS (HiSeq X™ trio) ($6556)



Estimates are given in 2018 Canadian dollars (CAD).

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

Figure 2. Present value of program costs over five years for CMA, WES (HiSeq® 2500/NextSeq® 550), WGS – proband and trio (HiSeq X™).



Estimates are given in 2018 Canadian dollars (CAD). Program costs are based on 300 ASD cases annually for CMA, WES/WGS proband tests and 900 ASD cases annually for WGS-trio tests. Confidence bands are based on 10,000 Monte Carlo replications.

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 (diagnosis rate)	Incremental ratio (CAD/diagnosis rate)
1. CMA+WES vs. CMA			
1.1 CMA+WES (HiSeq® 2500) vs. CMA	1960 (1899, 2020)	0.065	$30,154
1.2 CMA+WES (NextSeq® 550) vs. CMA	1981 (1909, 2054)	0.065	$30,471
2. WGS vs. CMA			
2.1 WGS-proband (HiSeq X™) vs. CMA	2526 (2404, 2648)	0.081	$31,260
2.2 WGS-trio (HiSeq X™) vs. CMA	5732 (5451, 6008)	0.101	$56,860
3. WGS-proband vs. CMA+WES			
3.1 WGS-proband (HiSeq X™) vs. CMA+WES (HiSeq® 2500)	566 (430, 704)	0.0158	$35,810
3.2 WGS-proband (HiSeq X™) vs. CMA+WES (NextSeq® 550)	545 (405, 689)	0.0158	$34,506
4. WGS-trio vs. CMA+WES			
4.1 WGS-trio (HiSeq X™) vs. CMA+WES (HiSeq® 2500)	3772 (3489, 4056)	0.0358	$105,349
4.2 WGS-trio (HiSeq X™) vs. CMA+WES (NextSeq® 550)	3751 (3460, 4041)	0.0358	$104,774

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

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

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