The Hospital for Sick Children

Technology Assessment at SickKids (TASK)

MICROCOSTING OF WHOLE GENOME SEQUENCING (WGS) OF TRIOS IN A HETEROGENEOUS PEDIATRIC CARDIAC POPULATION

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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

Cardiomyopathies (CMP), congenital heart defects (CHD) and inherited cardiac arrhythmias such as cardiac channelopathies can cause heart failure in pediatric and adult populations. Genetic variants and epigenetic changes may explain clinical phenotypes that are challenging to diagnose, treat, and manage. Whole genome sequencing (WGS) has the potential for increased diagnostic accuracy as well as improved management and care. WGS provides detailed information about a patient's genome by detecting small and large *de novo* and inherited variations in coding and noncoding regions of DNA (1, 2). It also helps identify pharmacogenomics variants associated with medication metabolism or sensitivities (3).

Key Messages

- The total cost per WGS-trio in Year 1 was $8053 (95% CI: 7700, 8558). Supplies comprised half and bioinformatics 25% of the total cost.
- Estimated total five-year program cost for WGS-trio tests was $5.63 million (95% CI: 5.38, 5.98) based on 144 CGC cases (48 families). The largest cost component was supplies.
- Costing of WGS is condition-specific.
- This study provides comprehensive cost data for use in future economic evaluations of clinical GS in various pediatric cardiac populations, and allows for a costing model that can be easily adapted to other pediatric patient populations in different health systems.

In precision medicine, optimizing diagnosis, management and care choices depend not only on clinical outcomes but also on economic value. Policy and reimbursement decisions regarding WGS as a health technology should take into consideration both clinical and economic evidence. While the laboratory costs of sequencing have decreased dramatically in recent years (4, 5), there is a paucity of studies that comprehensively estimate actual test costs. Full economic evaluation of WGS technology that weigh the incremental costs of WGS against its incremental benefits to patients require accurate estimations of all costs involved in the workflow (6).

Objectives

The objective of this study was to estimate the precise cost per trio for WGS using a microcosting approach for a targeted patient population consisting of children with CHD, cardiac arrhythmia or CMP. In the microcosting approach, the volume of use and unit price of each resource use component was estimated (7) and the entire workflow process of a genetic test was tracked. This microcosting study did not include consideration of diagnostic yield or other lab performance metrics.

Methods

Using a bottom-up microcosting approach, the opportunity cost per trio excluding mark-ups, fees and charges for WGS tests for patients with a range of cardiac conditions was estimated for each component in the workflow process. This was done from an institutional payer perspective based on the diagnostic laboratory practices at SickKids, Toronto, Canada. In addition to WGS, analysis of pharmacogenomics variants was performed. This analysis followed the guidelines of The Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and other professional societies (8) and was conducted in probands (patients) in contrast to WGS analysis which was done on trios. Only the variants with level 1A clinical annotation published on the curated PharmGKB database were analyzed (9). Pharmacogenomics testing was done outside of SickKids. Secondary variants as per ACMG guidelines (10) were identified and confirmatory testing was done by a lab outside of SickKids.

The total cost per trio was determined for each year of a five-year program. Total SickKids program costs to service the pediatric cardiac patient population were also estimated over five years. In order to conduct probabilistic analysis (PA) for each input's resource use and unit price, a range and probability distribution was established in consultation with experts. Probability distributions were defined for inputs which were either proportions or for which upper and lower bound were provided in addition to a point estimate. Since no evidence existed for any specific form of correlation, all input distributions were assumed to be independent. To propagate variability in the model, 10,000 values were drawn from each input's distribution (i.e. confidence intervals using Monte Carlo replications). Point estimates of inputs with fixed

values, i.e. inputs for which ranges were not provided, were repeated 10,000 times. Three one-way deterministic sensitivity analyses (DSA) were conducted to examine the effects of changing the following inputs while other input parameters remained the same: i) the overhead cost; ii) the total volume of tests in the institution; and iii) omission of pharmacogenomics. These DSAs permitted an examination of how changing the values of uncertain inputs one at a time affected the results.

Results

The results of WGS-trio (HiSeq X™) microcosting analysis are shown in Table 1. The total estimated costs per trio for each year of the five-year program are shown, as well as costs for major cost categories. Figure 1 shows the distribution of the cost per trio by cost category. The results were based on reference values for overhead costs (22.3%) and the number of total tests assumed per year in the institution for all indications (1500).

The total cost per WGS-trio in Year 1 was $8053.10 (95% CI: 7699.30, 8558.10). Supplies made up 50.8% of the total costs whereas bioinformatics accounted for 24.8% of the costs. Labour, overhead, confirmatory testing and large equipment accounted for 11.2%, 8.5%, 2.4% and 2.3%, respectively. Small equipment had a contribution to the overall cost of < 1% (Figure 1).

The estimated total institutional program cost for the WGS-trio tests over the five-year period based on 144 Cardiac Genome Clinic (CGC) cases (48 families) per year on the HiSeq X™ platform was $5.63 million (95% CI: 5.38, 5.98). Figure 2 shows the program costs for each cost component of the trio test. The equipment component included the cost of both small and large equipment. The program cost of supplies was the largest among the six cost components.

Discussion

In this study, the trio and program costs of WGS genetic tests for children with cardiac disorders in the CGC were estimated. Primary determinants of costs were supplies and bioinformatics, which together accounted for 75% of the total cost. This is due to the greater consumption of costly reagents required for sequencing trios. Similarly, computing demands are much higher for trios. Labour cost was comprised of ten

components. Of these components, bioinformatics, clinical interpretation, case review and pharmacogenomics analysis were the most costly due to time invested.

The present microcosting model incorporated the pharmacogenomics component that provides information on how specific genetic variants may be responsible for metabolism of certain classes of medications. Furthermore, pharmacogenomics provides information to suggest alternate medications for the disease/condition of interest. The pharmacogenomics analysis also looks into additional haplotypes and phenotypes (3). The present model included ten cardiac genes for which there may be medication implications and the cost of this analysis was $389 per proband. If the list of the genes is expanded, then the cost of pharmacogenomics analysis is likely to increase.

The study has several strengths. All stages and costs involved in the workflow of WGS-trio were accounted for using the microcosting approach generating fully comprehensive per trio and program cost estimates. Uncertainty associated with parameter estimates was captured in the PA using Monte Carlo simulations. Parameters that were highly uncertain or expected to vary substantially between institutions were varied in DSA demonstrating robustness of the results to changes in assumptions. Predicting costs and volumes of use before a technology has been clinically established presents certain challenges. This study showed how economies of scale can be realized to reduce the trio costs as the volume of total WGS tests increases, in advance of full implementation. The level of this economic efficiency may be different between a proband and trio sequencing as the trio cost is substantially more costly compared to the proband cost. The study also showed where cost savings can be realized. Omitting pharmacogenomics analysis is a potential option if it is not expected to be of value for certain indications, if there is limited funding, or if the labour, supplies and the computing demands for this analysis are deemed to be too costly. The additional cost involved in identifying and confirming secondary variants is a small component of the total cost and therefore unlikely to be a major cost contributor. Identification of secondary variants however has potentially significant downstream effects on use of health resource and the potential for additional health benefits which require further study. Although the estimates in this report are for a pediatric cardiac patient population, the microcosting model was deliberately constructed to be flexible and easily adaptable to other patient populations by changing the resource use items and the volume of testing in the institution. The present model was adapted from a microcosting model for ASD (11, 12).

This study has several limitations. For most of the price parameters, a range of 10% was not based on an expert opinion, but instead chosen to reflect potential price and currency fluctuations. Nevertheless, this range was within the variation for other parameters reported by experts. A five-year time horizon was chosen based on a projected shelf-life for the sequencing equipment, and because procurement decisions for large equipment can be based on a five-year budget plan. In reality, the life cycle for sequencers may be shorter due to rapid evolution of the sequencing hardware and software combined with the frequency of usage. A shorter life cycle would result in higher costs due to a shorter period of amortization. This evaluation did not capture any outcomes such as diagnostic yield or change in clinical management. When measured and captured in future studies, these outcome data would enable a cost-effectiveness analysis (CEA) or cost-consequence analysis (CCA). Another limitation is that this study modelled a trio involving the proband and both biological parents as recommended in clinical practice and does not include estimates for sequencing a duo or proband which may also occur. Furthermore, clinical consultations, genetic counselling and delivery of results to patients and parents were not captured.

Costing of WGS will likely prove to be condition-specific. However, this heterogeneous pediatric cardiac disease population represents a patient group with serious, potentially fatal conditions that impose significant burdens on families and the health care system. Findings from this study may be relevant to designing future evaluations in other patient populations and in other jurisdictions. Patients and parents who were modeled in this study may not be fully representative of the population as a whole. However, establishing the ability to track health care resource use and costs is an essential first step towards generating more generalizable data as it allows researchers to better understand the resource use implications of genetic and genomic testing and facilitates future comparative economic evaluation to inform future clinical, policy and funding decision-making.

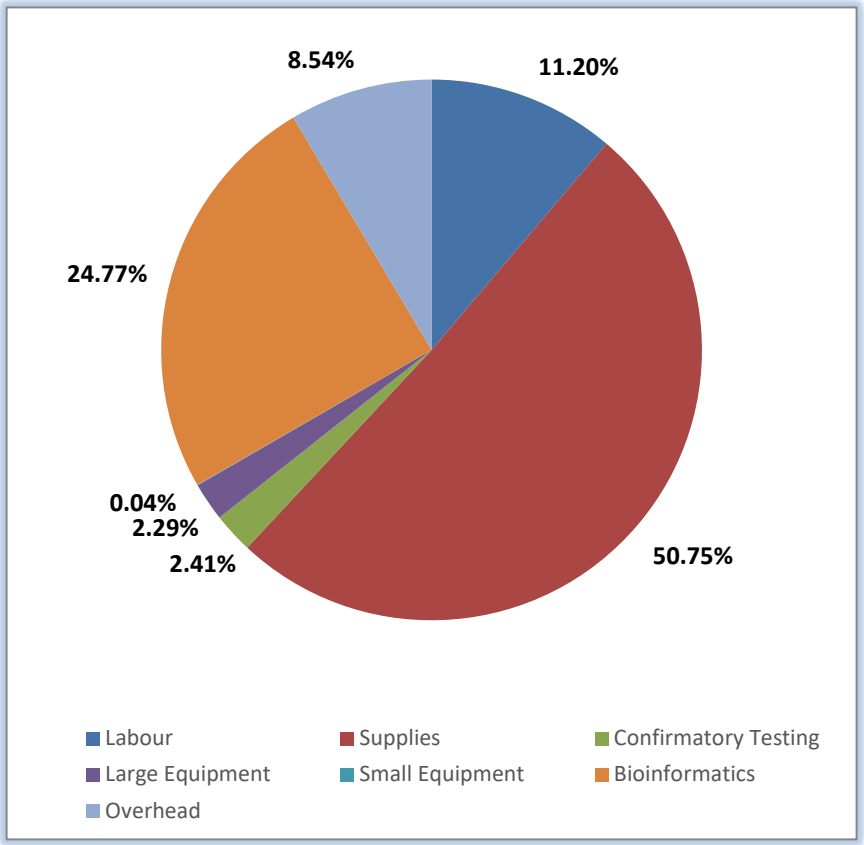
Table 1. Estimated Annual Cost per Cardiac Genome Clinic Trio for Whole Genome Sequencing (Illumina HiSeq X™)

Cost Category	Year 1 (95% CI)	Year 2 (95% CI)	Year 3 (95%CI)	Year 4 (95% CI)	Year 5 (95% CI)
Labour	900.50 (760.20, 1261.20)	887.20 (749.00, 1242.50)	874.10 (737.90, 1224.20)	861.10 (727.00, 1206.10)	848.40 (716.30, 1188.30)
Large Equipment	184.70 (174.00, 195.60)	179.40 (169.00, 190.00)	174.30 (164.10, 184.60)	169.20 (159.40, 179.20)	164.30 (154.70, 174.00)
Small Equipment	3.00 (2.90, 3.10)	2.90 (2.80, 3.00)	2.90 (2.80, 3.00)	2.80 (2.70, 2.90)	2.80 (2.70, 2.90)
Supplies	4088.00 (3840.60, 4333.20)	4027.60 (3783.90, 4269.20)	3968.00 (3727.90, 4206.10)	3909.40 (3672.80, 4143.90)	3851.60 (3618.60, 4082.70)
Confirmatory Testing	194.40 (149.40, 250.00)	191.50 (147.20, 246.30)	188.70 (145.00, 242.70)	185.90 (142.90, 239.10)	183.10 (140.80, 235.60)
Bioinformatics	1995.00 (1900.60, 2091.70)	1965.50 (1872.50, 2060.80)	1936.50 (1844.90, 2030.40)	1907.90 (1817.60, 2000.40)	1879.70 (1790.70, 1970.80)
Overhead	687.50 (646.90, 768.80)	676.80 (636.80, 756.90)	666.30 (626.80, 745.20)	655.90 (617.00, 733.70)	645.60 (607.30, 722.30)
Total	8053.10 (7699.30, 8558.10)	7931.00 (7582.40, 8428.40)	7810.70 (7467.30, 8300.80)	7692.30 (7353.90, 8175.10)	7575.60 (7242.20, 8051.40)

Estimates are given in 2019 Canadian dollars (CAD). Confidence intervals (CI) are based on 10,000 Monte Carlo replications. The results were based on reference levels for overhead costs of 22.3% and 1500 total tests done for all indications per year.

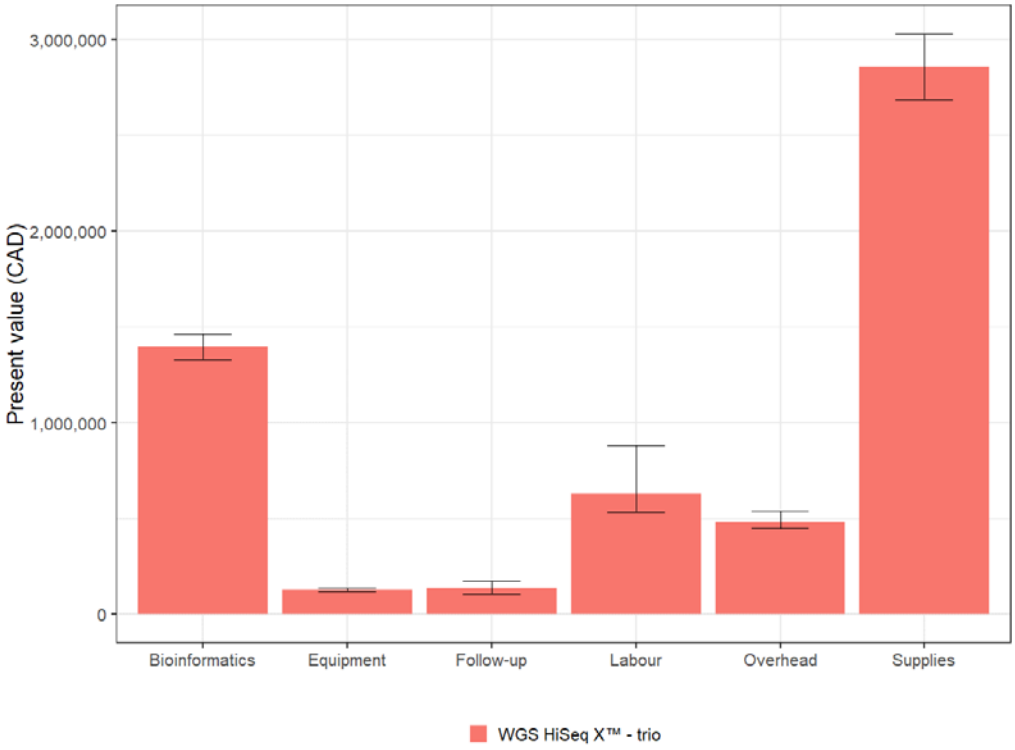
Abbreviations: CGC, Cardiac Genome Clinic; WGS, Whole genome sequencing.

Figure 1. Proportion of Total Annual Cost for Cardiac Genome Clinic Whole Genome Sequencing - trio (Illumina HiSeq X™) by Cost Category, Year 1.



Estimates are given in 2019 Canadian dollars (CAD); Abbreviations: WGS, Whole genome sequencing.

Figure 2. Present Value of Program Costs Over Five Years for Whole Genome Sequencing – trio (HiSeq X™).



Estimates are given in 2019 Canadian dollars (CAD). Program costs are based on 144 CGC cases annually for WGS-trio tests. Confidence bands are based on 10,000 Monte Carlo replications.
Abbreviations: CGC, Cardiac Genome Clinic; WGS, Whole genome sequencing.

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