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SHORT COMMUNICATION

Determining accurate costs for genomic sequencing technologies—a necessary prerequisite

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Abstract

Genome sequencing (GS) is increasingly being translated into clinical practice and is a technology characterized by a complex multi-step workflow. Funding decisions for GS would be aided by formal economic evaluation of GS platforms, but these analyses require detailed costing. This article addresses the importance of and challenges associated with costing GS using a GS microcosting project in autism spectrum disorder as an illustrative example.

Keywords Genome sequencing · Chromosomal microarray · Health technology assessment · Economic evaluation · Microcosting · Autism spectrum disorder

Faced with a growing demand for genome sequencing (GS) by patients and clinicians, health plan decision-makers in the USA, Canada, the UK, and elsewhere are grappling with how to evaluate and fund these technologies as they emerge into practice (Weymann et al. 2019). The need for valid, high-quality evidence of economic value is essential in the face of pseudo-economic claims regarding affordability (e.g., "the $1000 genome") and falling costs that have been used to mislead decision-makers (Phillips et al. 2015). The ideal means to generate such evidence is through health technology assessment (HTA). HTA aggregates evidence on the clinical validity, safety, clinical utility, and ethical, legal, and social aspects of emerging technologies. At its core, HTA includes a formal cost-effectiveness analysis that compares the new technology to an existing standard.

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Sequencing costs and health technology assessment

Precise and detailed costing is a necessary prerequisite for economic evaluation of GS. The goal of economic evaluation is to understand the marginal effect, i.e., the incremental costs (or savings) of GS compared with a standard of care, and what this additional investment buys in added benefit. "Benefit" may be expressed in terms of clinical utility and test effectiveness, e.g., diagnostic yield, but preferably is expressed as improvements in a patient's health status that arise as a consequence of changes in a patient's management prompted by GS (CADTH 2017). Understanding the longer-term effects on health is the ultimate objective for funding decision-makers but such data are rarely available for emerging diagnostic technologies.

A review by Schwarze et al. (2018) summarized available health economic evidence on whole exome (WES) and whole genome sequencing (WGS) (Schwarze et al. 2018). Of the 36 studies reviewed, 26 studies evaluated WES and/or WGS in multiple diseases such as cardiomyopathy and pediatric neurological disorders. Nineteen studies were either full or partial economic evaluations while seven were cost studies. All studies were done in the USA, the UK, Canada, Australia, or other European countries. The primary comparator for WES/WGS was the conventional testing pathway that included molecular and/or cytogenetic tests. Cost estimates from eighteen studies

investigating WES ranged from $555 to $5169 USD for singletons and $3825 to $9304 for trio-based studies. Cost estimates from six WGS studies ranged from $1906 to $24,810 USD. Variation observed was attributable to the price used (opportunity cost or commercial price), the costing approach (e.g., microcosting or gross costing), the source of the cost data, or the cost components that were included (Schwarze et al. 2018). Only four studies used a transparent microcosting approach, emphasizing the scarcity of accurate and precise costing of these technologies (Schwarze et al. 2018).

Challenges in costing genomic technologies

While gross costing using charges or estimates of total costs has been used in economic evaluation of GS (Buchanan et al. 2013), in reality, GS is a technology that is comprised of a complex workflow, each consisting of numerous separate cost items. Microcosting identifies the types, quantities, and the associated component costs of resources related to a particular intervention (Jani et al. 2016). When applied to WES/WGS, it allows for the entire workflow to be tracked. Moreover, microcosting promotes transparency and allows for individual items to be updated as the technology evolves. As an example of a microcosting project, our team conducted microcosting to estimate the per sample costs of various GS platforms used to aid a diagnosis of autism spectrum disorder (ASD). The laboratory workflow from blood draw to laboratory reporting was broken down into steps, and within each step, every resource was itemized, resulting in a total number of microcost items that ranged from 38 for chromosomal microarray (CMA) to 68 for WES-HiSeq® 2500. All items were categorized as labor, supplies, follow-up testing, bioinformatics, and small or large equipment (Jegathisawaran et al. 2018).

The first GS microcosting was conducted by our team in 2016 and analyzed probands only (Tsiplova et al. 2016; Tsiplova et al. 2017). The cost model was deliberately built to enable easy updating in recognition of rapidly changing GS technologies. An update was performed in 2018 to capture advances in procedures and technology, update inputs including labor costs for all platforms, and add trio-based evaluation (child and two parents) for WES and WGS (Jegathisawaran et al. 2018). The detailed methods for estimating costs of trio WES/WGS and the methodological differences between the original and updated microcosting studies are outlined elsewhere (Jegathisawaran et al. 2018). While trio sequencing can enhance the ability to detect variants of interest as well as determine genetic profiles for parents, it further complicates economic evaluation with regard to the scope of downstream health and cost consequences that should be captured. The results per ASD sample for both probands and trios in each of the platforms are displayed in Table 1. There is no evidence that costs have decreased since 2016. Differences between 2016 and 2018 estimates are due to additional bioinformatics processing steps, updated wage information, and increased reagent costs (for HiSeq® 2500) (Jegathisawaran et al. 2018; Tsiplova et al. 2016).

There are several challenges to microcosting a GS technology. Rapid evolution of sequencing technology and platforms makes it challenging to maintain up to date, accurate, and precise costs. Changes in computational capacity, software, and requirements, in addition to the upgrades in equipment and procedures within and between institutions, contribute to this challenge. As WGS is mainly a research application, calculating opportunity costs to reflect a clinical rather than a research context can be informed by WES microcosting but also may require expert opinion. Hence, the actual costs of WGS may diverge from projected estimates when introduced in clinical settings. An opportunity cost approach using microcosting may nevertheless be superior to applying fixed charges from an external service provider as it avoids mark-ups and commercial pricing. Furthermore, microcosting is institution-specific. The selected input parameters may differ between settings. Equipment supply costs and maintenance contracts can be negotiated, resulting in differences between institutions. Taking a probabilistic approach to microcosting that models ranges for each cost item to reflect variation across institutions allows for price and volume uncertainty to be directly incorporated into the point estimates and enables the calculation of confidence intervals around cost estimates for regional decision-making.

In conclusion, precise estimates of the costs associated with GS platforms are a prerequisite to full economic evaluations essential for informing coverage decisions and policy as these new technologies are translated into clinical practice. As illustrated by work in our institution, efforts to standardize procedures, such as patient consent, bioinformatics pipelines, and laboratory processes, will impact the efficiency and the ultimate cost of the workflow (Weymann et al. 2019). Changes in sequencing platforms and the removal of older obsolete platforms will impact the quality of the data generated and the associated costs. Discovery of new genetic variants and their linkage to disease mechanisms is proceeding at an astonishing rate, creating pressure to introduce GS into clinical practice as a funded healthcare service. Improvements in sequencing technologies will continue to occur alongside the early stages of clinical implementation, necessitating periodic updates to studies of costs, clinical utility, and cost-effectiveness.

Table 1 Estimated annual cost per sample for different genetic testing platforms for proband and for trio in children with autism

Cost category	Chromosomal microarray (95% CI)	Whole exome sequencing			
		Hi Seq® 2500		Next Seq® 550	
		Proband (95% CI)	Trio (95% CI)	Proband (95% CI)	Trio (95% CI)
Labor	151.30 (139.30, 163.50)	506.30 (465.10, 546.70)	688.50 (647.90, 729.50)	499.80 (457.80, 544.20)	656.40 (616.70, 697.50)
Large equipment	50.10 (47.10, 53.10)	385.50 (370.00, 400.90)	128.50 (123.30, 133.60)	115.10 (109.00, 121.20)	38.40 (36.30, 40.40)
Small equipment	N/A	8.80 (8.50, 9.10)	2.90 (2.80, 3.00)	8.80 (8.50, 9.10)	2.90 (2.80, 3.00)
Supplies	501.20 (470.30, 531.10)	643.20 (617.90, 668.20)	1929.60 (1854.20, 2004.70)	1002.70 (955.90, 1048.40)	3008.00 (2865.50, 3147.30)
Follow-up	76.90 (69.10, 84.80)	155.40 (138.90, 173.00)	31.10 (26.20, 36.30)	155.30 (138.70, 172.40)	31.10 (26.20, 36.40)
Bioinformatics	N/A	49.10 (45.80, 52.30)	147.10 (137.40, 157.00)	49.00 (45.90, 52.30)	147.20 (137.40, 156.90)
Overhead	44.90 (42.10, 47.70)	211.80 (201.90, 221.50)	215.70 (206.20, 225.30)	150.00 (140.50, 160.10)	188.40 (179.30, 197.80)
Total	825.00 (789.00, 859.00)	1960.00 (1899.00, 2020.00)	3143.40 (3052.90, 3233.90)	1981.00 (1909.00, 2054.00)	4072.30 (3922.60, 4222.50)

Cost category	Whole genome sequencing	
	HiSeq X™	
	Proband (95% CI)	Trio (95% CI)
Labor	464.70 (417.20, 515.30)	473.70 (430.60, 520.50)
Large equipment	583.60 (549.80, 617.00)	194.60 (183.40, 206.10)
Small equipment	8.80 (8.50, 9.10)	2.90 (2.80, 3.00)
Supplies	1367.50 (1284.50, 1448.90)	4099.90 (3847.70, 4348.80)
Follow-up	177.00 (159.00, 195.40)	96.20 (87.80, 104.80)
Bioinformatics	419.40 (390.60, 449.10)	1258.30 (1172.80, 1346.70)
Overhead	329.30 (314.50, 344.10)	430.30 (408.50, 452.40)
Total	3350.00 (3234.00, 3467.00)	6556.00 (6278.00, 6832.00)

Trio is defined as child and two parents. Estimates based on overhead costs of 22.3%, 500 total tests for probands, and 1500 total tests for trios done for all indications per year, and an average of two primary variants found per test. Confidence intervals (CI) are based on 10,000 Monte Carlo replications

All estimates are given in 2018 Canadian dollars (CAD)

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Compliance with ethical standards

The authors declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the any of the authors.

References

Buchanan J, Wordsworth S, Schuh A (2013) Issues surrounding the health economic evaluation of genomic technologies. Phamacogenomics 14:1833–1847. https://doi.org/10.2217/pgs.13.183

CADTH (2017) Guidelines for the economic evaluation of health technologies: Canada. 4th ed. CADTH, Ottawa

Jani M, Gavan S, Chinoy H, Dixon WG, Barton A, Harrison B, Moran A, Barton A, Payne K (2016) A microcosting study of immunogenicity and tumour necrosis factor alpha inhibitor drug level tests for therapeutic drug monitoring in clinical practice. Rheumatology 55:2131–2137. https://doi.org/10.1093/rheumatology/kew292

Jegathisawaran J, Tsiplova K, Marshall CR, Stavropoulos DJ, Pereira S, Thiruvahindrapuram, B, Ungar WJ (2018) A microcosting and cost-consequence analysis of genomic testing strategies (including trios) in austim spectrum disorder: an update. http://lab.research.sickkids.ca/task/reports-theses/. Accessed 14 Feb 2019

Phillips KA, Pletcher MJ, Ladabaum U (2015) Is the "$1000 genome" really $1000? Understanding the full benefits and costs of genomic sequencing. Technol Health Care 23:373–379. https://doi.org/10.3233/THC-150900

Schwarze K, Buchanan J, Taylor JC, Wordsworth S (2018) Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med 20:1122–1130. https://doi.org/10.1038/gim.2017.247

Tsiplova K, Zur RM, Ungar WJ, Marshall CR, Stavropoulos DJ, Pereira SL, Merico D, Young EJ, Sung WWL, Scherer SW (2016) A microcosting and cost-consequence analysis of genomic testing strategies in autism spectrum disorder. http://lab.research.sickkids.ca/task/reports-theses/. Accessed 18 May 2016

Tsiplova K, Zur RM, Marshall CR, Stavropoulos DJ, Pereira SL, Merico D, Young EJ, Sung WWL, Scherer SW, Ungar WJ (2017) A microcosting and cost–consequence analysis of clinical genomic testing strategies in autism spectrum disorder. Genet Med 19:1268–1275. https://doi.org/10.1038/gim.2017.47

Weymann D, Dragojlovic N, Pollard S, Regier DA (2019) Allocating healthcare resources to genomic testing in Canada: latest evidence and current challenges. J Community Genet:1–10. https://doi.org/10.1007/s12687-019-00428-5