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SYSTEMATIC REVIEW

Microcosting diagnostic genomic sequencing: A systematic review

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ABSTRACT

Purpose: Microcosting can provide valuable economic evidence to inform the translation of genomic sequencing to clinical practice. A systematic literature review was conducted to identify studies employing microcosting methods to estimate the cost of genomic sequencing to diagnose cancer and rare diseases.

Methods: Four electronic databases, Medline, Embase, EconLit, and Cumulated Index to Nursing and Allied Health Literature were searched. Reference lists of identified studies were also searched. Studies were included if they had estimated the cost of genome sequencing or exome sequencing for cancer or rare disease diagnosis using microcosting methods.

Results: Seven studies met the inclusion criteria. Cost estimates for genome sequencing and exome sequencing ranged between US$2094 and $9706 and US$716 and $4817 per patient, respectively. All studies disaggregated resource use and cost inputs into labor, equipment, and consumables, with consumables being the main cost component. Considerable differences in the level of detail used to report the steps and resources used in each of the sequencing steps limited study comparisons.

Conclusion: Defining a standard microcosting methodology is challenging because of the heterogeneous nature of genomic sequencing. Reporting of detailed and complete sequencing procedures, inclusion of sensitivity analyses and clear justifications of resource use, and measurement of unit costs can improve comparability, transferability, and generalizability of study findings.

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Introduction

Rare diseases pose a substantial burden to public health and health care systems. They affect an estimated 380 million children and 95 million adults globally,[1,2] accounting for approximately 35% of mortality in newborns.[1] Collectively, rare diseases represent close to a third of pediatric health spending in Canada[3] and a total economic burden of $997 billion dollars in the United States.[4] Genomic sequencing can end diagnostic odyssey and provide economic benefits to health care systems.[5,6] Clinical, personal, and process outcomes for people affected by rare disease and their families[7,8] are highly valued on average by the society and people with lived experiences of rare disease and cancer.[6,9] Nevertheless, concerns with data privacy, evidentiary uncertainty, and additional findings still pertain.[9]

Genomic sequencing is now being embedded in many health care systems around the world,[5] but affordability concerns and limited cost-effectiveness evidence have been key implementation barriers.[10-12] Accurate and generalizable information related to the cost of delivering genomic testing, economic implications associated with the tests' clinical utility, and opportunity cost of testing are essential in guiding decision-making priorities and appropriately informing sustainable national clinical implementation.[13-15] However, cost reporting is identified as a major quality issue in published economic evaluations.[11] The need for studies applying microcosting methods to estimate the economic cost of genomic sequencing by identifying and valuing all health care resources required and the associated unit costs is now recognized because of the complex variations in generating and interpreting genomic data.[5,10,16]

This article reports the findings from a systematic review of studies using microcosting methods to estimate the cost of genomic sequencing for rare disease and cancer diagnosis. This systematic review aimed to identify key resource use items and unit costs included in the costing methodologies, explore analytical approaches used to estimate costs and account for uncertainty, and appraise the comparability and generalizability of the estimates. This review provides insights into the current literature to guide future microcosting studies of clinical and functional genomics, enabling consistency in the collection and analysis of relevant resource use and unit cost data.

Materials and Methods

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020)[17] and Cochrane Handbook for Systematic Reviews of Interventions[18] guidelines for conducting and reporting systematic reviews.

Overview

This review systematically identified studies that applied microcosting methods to estimate the cost of genome sequencing (GS) and exome sequencing (ES), from sample preparation to variant classification report, used for diagnostic purposes. The main objective of the systematic review was to collate evidence for the total cost of sequencing across clinical indications, key resources considered, and analytical methods used.

Search strategy

In consultation with the Biosciences research liaison librarian from the University of Melbourne, search strategies were developed for 4 databases: Medline (including Epub ahead of print, in-process, in-data-review, and other nonindexed citations and daily); Embase, accessed via the Ovid platform; and EconLit and Cumulated Index to Nursing and Allied Health Literature, accessed from the EBSCOhost research platform. The search syntax was structured to include genomics and sequencing concepts in line with the published literature,[7,10,11,16] with microcosting terms being drawn from a systematic review of microcosting studies in the health and medical literature.[19] The final search string included free-text words and Medical Subject Headings combined using Boolean operators (AND, OR) (Appendices 1-4). There were no restrictions imposed in the search strategy. References from included studies were additionally screened.

Study selection

The searches were finalized on March 30, 2022 for all databases. The search results were exported to the Covidence systematic review software (Veritas Health Innovation). After removing duplicates, screening of titles and abstracts was performed independently by 2 researchers (F.S.G. and D.M.) based on the population, interventions, comparators, and outcomes (PICO) framework (Table 1). This was followed by 2 independent full-text reviews (F.S.G. and D.M.) using the same PICO framework for the inclusion/exclusion criteria. Disagreement was resolved through discussions with the wider research team.

To be included in the review, studies had to use microcosting methods to estimate the cost of either GS or ES in the context of the identification of pathogenic variants in cancer or rare disease diagnosis. Examples of such procedures include ES for neurodevelopmental disorders of unknown genetic etiology or GS of tumor and germline samples from patients with colorectal cancer.

A study from 2005[20] was excluded during the screening process because it considered chain-termination sequencing, a first-generation DNA sequencing technique. The technological capabilities of sequencing have improved over time while also becoming more affordable, making it possible to

Table 1 Population, interventions, comparators, and outcomes criteria

Category	Details
Population	• Adult and pediatric patients with rare genetic disorders (or suspected rare genetic conditions) • Adult and pediatric patients with cancer for whom an identification of pathogenic variants is sought
Intervention	• Genome sequencing or exome sequencing
Comparator	• Not applicable
Outcomes	• Cost of diagnostic test per patient or trio • Cost categories • Input costs • Sensitivity analysis • Main cost components
Study designs	• Microcosting studies • Bottom-up and top-down costing
Language	• No restriction
Country	• No restriction
Date of publication	• No restriction

read DNA with hundreds of base pairs in length and generate gigabytes of data in a single run.[21] Studies addressing other types of genetic testing including panel tests, arrays, or those primarily used for molecular-guided therapy were also excluded.

Data extraction

A data extraction template was designed using the Covidence software, which 2 researchers (F.S.G. and D.M.) used to perform independent data extractions. The extracted data were compared, and discrepancies were resolved through discussion with all coauthors. The collected data included bibliographic details, sample size, study setting, resources measured and valued, source for unit costs, data analyses, total costs, and currency and year.

Classification of results

Selected publications were classified according to the clinical area (cancer or rare diseases) and sequencing procedure (GS or ES), noting differences in sequencing depth/coverage and the sequencing platform used. Information about sequencing workflows and protocols, microcosting approaches (eg, bottom-up or top-down microcosting), sensitivity analyses, and additional considerations, such as the inclusion of discount rates, overhead and data archiving costs, were also captured. These data points were cross tabulated to compare methodologies and resource categories across all papers (Appendix 5).

In a similar manner, the study setting, either research or clinical practice, as well as the conditions being diagnosed via sequencing were noted for each study. Information about study characteristics, such as process for resource item identification, source of unit costs, CIs and sample size, including any assumptions to estimate the number of samples considered for the calculation of sequencing costs were also collected.

Analysis of sequencing workflows

Sequencing process stages and other considerations for calculation of costs were reviewed for all papers. These included specific steps from sample preparation, bioinformatics, and data archiving to inclusion of overhead costs and discount rates. When required, cost estimates were converted to US dollars based on the respective yearly average exchange rate (www.xe.com) or according to the rate reported by the authors and inflated to 2021 US dollars using the GDP Price Deflator (U.S. Bureau of Economic Analysis).

Owing to the differences in protocols as well as sequencing depth/coverage for the different conditions for which a diagnosis was sought, it was not possible to calculate a representative average cost for all procedures. Costs estimates for ES and GS were classified according to clinical area and procedure and subclassified in a per patient basis for cancer, reflecting the need of either matched germline DNA and DNA extracted from a cancer sample or germline DNA only. In the case of rare diseases, estimates were classified per patient for singleton sequencing or per trio basis for families. Results were narratively synthesized in the results section.

Results

A total of 101 publications were identified from database searches. Eight additional potentially relevant studies were allocated after the database searches. After removing duplicates, 71 publications underwent independent title and abstract screening by 2 reviewers (F.S.G. and D.M.). A total of 15 publications were deemed irrelevant, with 56 full-text papers being assessed for eligibility based on the PICO criteria. The details of all excluded references, including the reason for exclusion are presented in Appendix 6. Overall, 7 papers met all eligibility criteria and were suitable for inclusion in this study. The selection process is summarized in Figure 1.

Study characteristics

The studies were published between 2016 and 2022 and more than half were conducted in Europe.[22-25] The rest of the publications came from North America[23,26] and Australia.[27] Of the studies selected for inclusion, 3 developed microcosting analyses for GS,[23,24,26] 2 microcosted ES,[22,28] and 2 studies used a microcosting approach for both GS and ES.[25,27] Table 2 summarizes key information from the included microcosting studies.

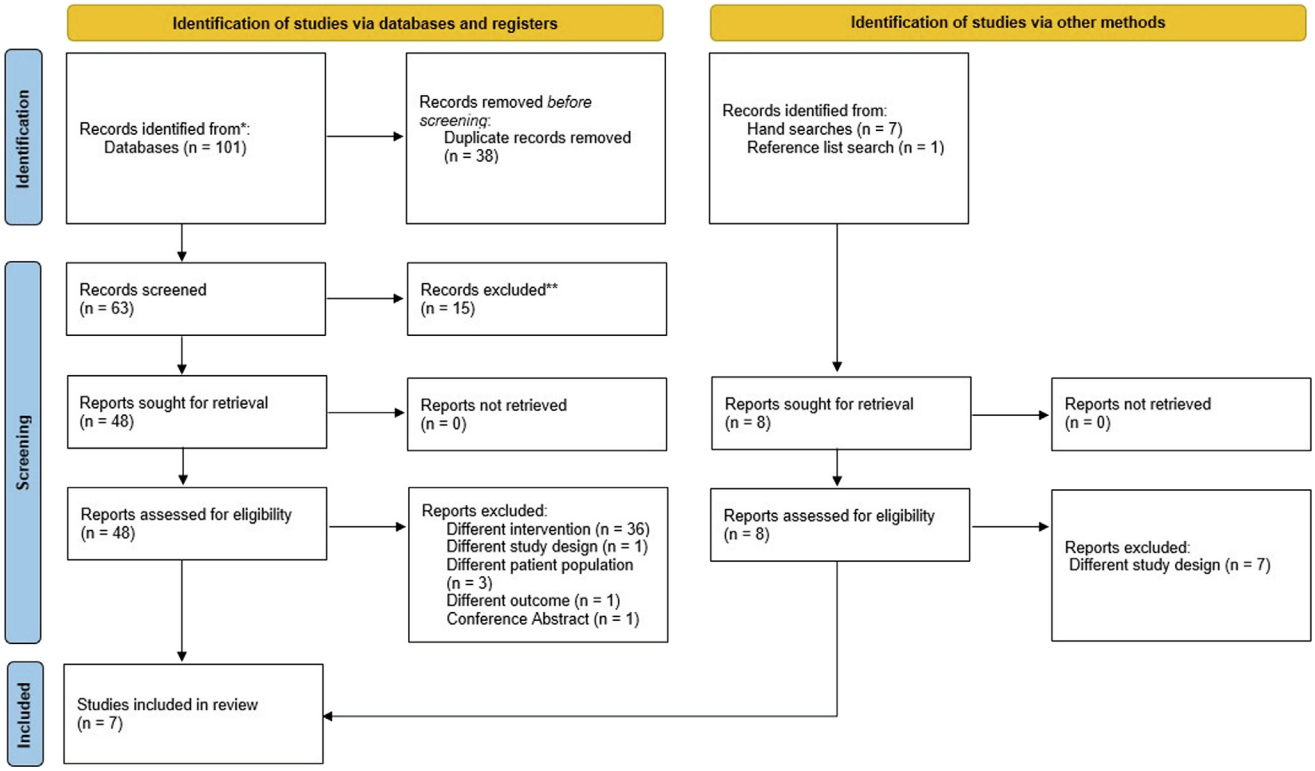

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the study selection process.

The papers provided cost estimates of sequencing for the diagnostics of rare diseases, including developmental disorders,[24,26,28] cardiac conditions,[24,26] and germline variants.[25] One study compared the costs of sequencing for cancer and rare disease diagnosis.[24] The rest provided cost estimates for different types of cancers, such as melanoma,[27] non–small cell lung cancer,[23] and solid tumors.[22]

Of the 5 studies that estimated the costs of ES and GS in clinical practice, 1 assumed hypothetical clinical application based on institutional capacity.[24] Two papers acknowledged that GS and ES are not currently available in routine clinical practice, therefore they considered research settings for their microcosting analyses.[22,26] There were some overlaps among 2 publications: the papers from van Nimwegen et al[25] and Bayle et al[22] used similar approaches to disaggregate and categorize the resource use items for each step in the sequencing workflow. Furthermore, they drew their base case assumptions to calculate costs from current clinical practice in Dutch medical centers. Nonetheless, all publications that met the eligibility criteria reported unique results and were therefore regarded as discrete studies.

Resource use items included

All studies considered 3 major resource use categories, namely costs of labor, equipment, and consumables, using a mix of bottom-up microcosting to disaggregate resource use and input costs, alongside top-down costing for overall expenditures such as overhead costs. Tasks and resources directly related to the sequencing process, including sample preparation and library preparation and validation, were also included in all analyses. Resource use related to equipment maintenance was also included in all papers with different considerations; 2 papers considered maintenance costs for the equipment used in the sequencing and bioinformatics steps.[23,26] The rest of the analyses considered maintenance costs for all equipment,[22,24,25] sequencing equipment only,[27] or the bioinformatics pipeline only.[28] The resources included in the studies for rare diseases were diverse. The study by Jegathisawaran et al[26] included a highly detailed breakdown of sequencing and bioinformatics steps such as equipment preparation, calibration, and quality controls. The authors also costed confirmatory testing via Sanger sequencing or quantitative polymerase chain reaction.

On the contrary, the microcosting analysis from Sabatini et al[28] only indicated general resource categories for the sample preparation and sequencing steps and grouping of the bioinformatics and reporting steps. Similarly, the study from van Nimwegen et al[25] provided only a topline overview of their sequencing workflows and it did not specify all the steps involved in preparing, sequencing, and analyzing their samples.

Schwarze et al[24] reported costs for both cancer and rare disease tests. The study was thorough in the resources included for sample and library preparation, sequencing, and bioinformatics steps, which were presented in detail. Although the study by Schwarze et al[24] did not consider the costs of confirmatory testing of primary and secondary

Table 2 Summary of study characteristics

Category	Subcategory	No. of Studies	Reference, First Author
Study setting	Australia	1	Gordon et al[27]
	Canada	1	Jegathisawaran et al[26]
	United Kingdom	1	Schwarze et al[24]
	The Netherlands	2	Pasmans et al[23]; van Nimwegen et al[25]
	France	1	Bayle et al[22]
	United States	1	Sabatini et al[28]
Year of publication	2016	2	Sabatini et al[28]; van Nimwegen et al[25]
	2020	2	Gordon et al[27]; Schwarze et al[24]
	2021	2	Bayle et al[22]; Pasmans et al[23]
	2022	1	Jegathisawaran et al[26]
Procedure	Exome sequencing	4	Sabatini et al[28]; van Nimwegen et al[25]; Gordon et al[27]; Bayle et al[22]
	Genome sequencing	5	van Nimwegen et al[25]; Gordon et al[27]; Schwarze et al[24]; Pasmans et al[23]; Jegathisawaran et al[26]
Clinical area	Cancer	5	Gordon et al[27]; Schwarze et al[24]; Bayle et al[22]; Pasmans et al[23]
	Rare diseases	4	Sabatini et al[28]; van Nimwegen et al[25]; Schwarze et al[24]; Jegathisawaran et al[26]
Context for cost estimation	Clinical practice	5	Sabatini et al[28]; van Nimwegen et al[25]; Gordon et al[27]; Schwarze et al[24]; Pasmans et al[23]
	Research project	2	Bayle et al[22]; Jegathisawaran et al[26]

variants included by Jegathisawaran et al,[26] it did include costs for error rates for each step of the process.

The studies that costed sequencing for cancer disaggregated resource use in a different manner. Two studies provided elaborate listings of resource items for DNA sample reception and processing and library preparation and validation along with brief details of the activities involved in sequencing and bioinformatics.[22,27] Similarly, Pasmans et al[23] included only general resource categories for sample preparation, sequencing, and bioinformatics, with insufficient detail on the specific tasks and resources involved in each step.

All studies considered costs for interpreting results and generating reports. Costs for data archiving were found in every study, either through a type of cost as storage cost per GB,[23,25-27] labor and software costs for data archiving[22,24] or alternatively as part of the bioinformatics validation and maintenance costs.[28] Two of the studies incorporated overhead costs as a percentage rate applied to equipment[26] or to the final costs.[24] The rest of the studies used different strategies such as considering procedural errors alongside inflated labor costs[27] or institutional overheads.[22,28] Two studies did not incorporate overhead costs.[23,25]

Costs of genomic sequencing

The cost of ES ranged from $716[27] to $4817[22] per patient for cancer testing. A detailed view of all included studies and their cost estimates is presented in Table 3. Cost estimates for GS ranged from $2236[27] for testing a patient with cancer to $9418 for rare disease trio-based testing. Consumables, in the form of plasticware, sample preparation kits, and sequencing reagents and kits, were persistently reported as the major contributors to total costs in most publications, presenting from 2%[27] up to 78%[23] of the total sequencing costs. Two studies[26,28] also mentioned bioinformatics and equipment as significant cost components, with 22% to 27% of total cost for GS rare disease trios[26] and 20% to 53% of the total cost for patient ES of rare diseases.[28] A detailed overview of the costs and proportion of total sequencing costs per costing category for all included papers is presented in Appendix 7.

Differences in cost estimates were noted across various conditions considered. The lowest cost per patient for ES ($716) was estimated for melanoma testing,[27] a procedure that included a single saliva sample in the NovaSeq 5000 sequencer (Illumina). In contrast, the cost of ES for lung cancer cases, which included a tumor and a blood sample sequenced on NextSeq 500 (Illumina), was estimated at $2219 per patient.[27] The highest cost for ES was $4817 per patient, which entailed tumor and nontumor tissue samples in patients with solid tumors using the HiSeq 2000 sequencer (Illumina).[22]

For rare diseases, 2 studies presented costs estimates of ES on different sequencing platforms. van Nimwegen et al[25] reported the cost of ES for germline variants at $993 per patient on HiSeq 4000 (Illumina). Sabatini et al[28] reported a higher variation of costs for ES using HiSeq (Illumina) and NextSeq (Illumina), ranging from $1499 to $3388 per patient for neurodevelopmental disorders of unknown genetic etiology.

Table 3 Summary of the primary information from the included studies

Year	2018	2018	2018	2018	2020	2015	2018	2016	2016	2016	2018	2018	2016	2016	2016	2015	2015
Level	Per patient	Per patient	Per patient	Per patient	Per patient	Per patient	Per patient	Per patient	Per trio	Per patient	Per trio	Per trio	Per patient	Per patient	Per patient	Per patient	Per patient
95% CI (USD 2021)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	(5048-5494)	(6119-6801)	NS	NS	NS	NS	NS
Original cost	AU$4923.53	AU$3006.65	AU$963	AU$2984.07	EUR€2925	EUR€3842	EUR€1608	GBP£6841	GBP£7050	GBP£2350	CAD$6634.11	CAD$8053.10	USD$3388.18	USD$2428.45	USD$1499.32	EUR€791.75	EUR€1669.02
Cost (USD 2021)	3661	2236	716	2219	3479	4817	2036	9418	9706	3235	5272	6400	3792	2718	1678	993	2094
MPS type, coverage, platform	GS, 30X blood, 60X tumor, Illumina HiSeq X Ten	GS, 28X blood, 50X tumor, BGI BGISEQ-500	ES, 100X, Illumina NovaSeq 5000	ES, 100-130X exome, 500-700X spiked-in gene panel, Illumina NextSeq 500	GS, 90X tumor, 30X blood, Illumina NovaSeq 6000	ES, 100X, Illumina HiSeq 2000	ES, 100X, Illumina NovaSeq 6000	GS, 30X DNA and 75X tumor, Illumina HiSeq 4000	GS, 30X, Illumina HiSeq 4000	GS, 30X, Illumina HiSeq 4000	GS, NS, Illumina HiSeq X Ten	GS/pharma cogenomics, NS, Illumina HiSeq X Ten	ES, NS (blood), Illumina HiSeq	ES, NS (blood), Illumina NextSeq	ES, NS (blood), Illumina HiSeq	ES, 70X, Illumina HiSeq 4000	GS, 30X, Illumina HiSeq X Five
Setting	Clinical practice				Clinical practice	Research project		Clinical practice			Research project		Clinical practice			Clinical practice	
Source of sample size	Data collected from 6 projects for genomic sequencing for patients with cancer				Estimated through standard case perspective (sample output in average laboratory practice)	Data obtained from project records		Data obtained from laboratory records			Estimation from total sequencing capacity and past testing volume		Estimated through the total output of laboratories performing sequencing			Annual throughput based on capacity and use	Annual throughput based on capacity and use
n	1433	1433	1433	1433	NS	1803		149	149		348		NS			7800	9801
Condition	Esophageal cancer	Mesothelioma	Melanoma	Lung cancer	NSCL, CRC, GIST	Solid tumors		Breast, colorectal, prostate, and endometrial cancers	Developmental, neurologic, immunologic, cardiovascular, and musculoskeletal conditions		Developmental delay	Cardiomyopathies, congenital heart defects, and inherited arrhythmias	Neurodevelopmental disorders of unknown genetic etiology			Germline variants	
Procedure	GS	GS	ES	ES	GS	ES	ES	GS	GS	GS	GS	GS	ES	ES	ES	ES	GS
Clinical area	Cancer	Cancer	Cancer	Cancer	Cancer	Cancer	Cancer	Cancer	Rare diseases	Rare diseases	Rare diseases	Rare diseases	Rare diseases	Rare diseases	Rare diseases	Rare diseases	Rare diseases
Reference	Gordon et al[27]	Gordon et al[27]	Gordon et al[27]	Gordon et al[27]	Pasmans et al[23]	Bayle et al[22]	Bayle et al[22]	Schwarze et al[24]	Schwarze et al[24]	Schwarze et al[24]	Jegathisawaran et al[26]	Jegathisawaran et al[26]	Sabatini et al[28]	Sabatini et al[28]	Sabatini et al[28]	van Nimwegen et al[25]	van Nimwegen et al[25]

AU, Australian dollar; *CAD*, Canadian dollar; *CRC*, colorectal cancer; *ES*, exome sequencing; *EUR*, Euro; *GBP*, British pound sterling; *GIST*, gastrointestinal stromal tumor; *GS*, genome sequencing; *MPS*, massively parallel sequencing; *NS*, not specified; *NSCL*, non–small cell lung cancer; *USD*, US dollar.

For GS, the lowest cost ($2094) was estimated for patient sequencing analyzing blood samples via HiSeq X Five sequencing (Illumina).[25] Other costs of GS for rare disease testing ranged from $3235[24] per patient to $5272 to $9706[24] for trio sequencing. The cost per trio sequencing for developmental delay was reported at $5272, (95% CI = $5048-$5494) and $6400 (95% CI = $6119-$6801) for cardiac conditions, such as congenital heart defects.[26] The highest overall cost for GS ($9706) was estimated for trio sequencing of developmental, neurologic, immunologic, cardiovascular, and musculoskeletal conditions using HiSeq 4000 sequencing.[24]

In the case of GS for cancer, Gordon et al[27] reported estimates of $2236 per patient for mesothelioma via BGI-SEQ-500 sequencing (BGI) and $3661 per patient for esophageal cancer on the HiSeq X Ten platform (llumina). Two other studies[23,24] analyzed the costs of ES in cancer. In the same way as Gordon et al,[27] both authors considered the use of tumor and germline samples but different sequencing equipment, NovaSeq 6000 (llumina) and HiSeq 4000, respectively. The studies reported costs between $3479 per patient for non–small cell lung carcinoma, colorectal cancer, and gastrointestinal stromal tumors[23] to $9418 per patient for breast, colorectal, prostate, and endometrial cancers.[24]

The study by Bayle et al[22] included an analysis of the cost differences of ES for patients with solid tumors in 2015 and 2018, comparing costs using the HiSeq 2000 (Illumina) platform in 2015 and the NovaSeq 6000 platform in 2018. The authors reported a decrease in total costs of 53% over the 3-year period when equipment costs fell from 16% to only 3% of total costs, whereas the cost of consumables increased by 12%. Furthermore, labor costs went up by 6%, which the authors attributed to additional time spent for library preparation because of the higher volume of samples that can be processed by the NovaSeq 6000 platform.

Analysis

The studies used different approaches to evaluate the net present value of future costs of GS and ES. One study[26] applied a 1.5% to 3% discount rate for all resource items alongside equipment depreciation via a straight linear method. Three studies considered a 3.5%[24,27] or 4.5%[25] discount rate over equipment lifespan, whereas 1 study used 5-year linear deprecation for equipment and a 3% interest rate for data archiving.[22] Two studies did not report the inclusion of discount or interest rates.[23,28]

Except for one of the publications,[28] all studies performed sensitivity analyses to evaluate the effect of variations in the costs of inputs, testing volumes, and other parameters. Most of the studies used fixed input values and conducted one-way deterministic sensitivity analysis (DSA) for a variety of cost components. These included overhead costs along with institutional volumes or diagnostic yields of sequencing tests[26] or sequencing platform use rates as well as fluctuations in unit costs of supplies and equipment useful life.[22] Other considerations included variations in sample throughput, consumables, data archiving, and labor-related costs, alongside equipment acquisition expenses as well as equipment lifespan or discount rates.[24,27] One study conducted a two-way DSA considering a simultaneous change in the use rates of the sequencing platforms and the costs of consumables.[23]

van Nimwegen et al[25] conducted one-way DSA to assess the effect of variations in sequencing depth, equipment use and lifespan, and costs of capital and consumables in their cost estimates for ES and GS. Furthermore, they analyzed best-case and worst-case scenarios to determine the extent of potential future cost reductions. In addition to the deterministic analysis highlighted above, Jegathisawaran et al[26] also reported a probabilistic analysis to incorporate parameter uncertainty. To this end, they assigned probability distributions to their inputs and used Monte Carlo simulations with 10,000 replications to generate a plausible range of values of cost estimates per trio GS.

Discussion

This review identified 7 publications using microcosting methods to estimate the cost of diagnostic ES and GS. Cost estimates ranged between $716 USD to $4817 USD per patient for ES and $2094 USD per patient up to $9706 USD per trio for GS.

In general, the identified studies used similar categories of resource use (eg, labor, equipment, and consumables). However, differences in the steps of the sequencing workflow process made it challenging to define a standard sequencing procedure for study comparison. Most studies built their workflow models based on the interviews with laboratory staff, reviews of the literature, and standard operating procedures from equipment suppliers. Three of the studies modeled their sequencing workflow by aggregating the protocols from external laboratories.[23,27,28] The importance of comprehensive costing approaches including detailed listings of resource use items cannot be overemphasized, because these are important steps to determine key cost components, resource use, and comparability of cost estimates.[29]

Consumables, including sample preparation and sequencing kits, sequencing reagents, and plasticware were reported as the largest cost component of genomic sequencing, representing up to 78% of the total costs of GS in patients with cancer[23] and 68% of GS of rare disease trios.[24] However, there were notable variations in the methodologies for data sourcing and additional considerations applied to the calculation of consumable costs. In most studies, unit costs for sequencing kits and reagents were obtained directly from supplier catalog prices or informed by laboratory staff interviews.[23,25-28] Two studies reported sourcing consumable costs from laboratory purchasing records but provided limited information on the considerations taken to reconcile their calculations of costs to price catalog values when purchasing in bulk quantities.[22,24]

These approaches might limit transparency regarding discount and special arrangements with suppliers that may inflate or discount the price of consumables. This discrepancy could lead to potential under or overestimation of consumable costs. Furthermore, the cost of consumables is volatile and susceptible to change because of regional market, supply chain and freight issues, as well as currency exchange rates.[26,29] Additional considerations that may influence differences in the cost of consumables are the inclusion of software costs[24] and shipping and handling of samples.[26]

Similarly, great variability was observed in the calculation of equipment costs. Overall, equipment costing was based on the amortization of the acquisition unit costs over their useful lifetime, which was subsequently used to calculate resource use through several approaches. These varied from a flat cost per test based on equipment use rates[25-27] to a stepwise costing per run or hour of equipment use.[22-24,28] Additional cost elements such as maintenance costs and overheads were inconsistently included in the calculation of equipment costs. Moreover, the considerations of equipment use rates varied from 50%[28] to 90%,[23] impacting the comparability of equipment costs. Finally, despite all studies reporting annual staff costs as personnel salaries, the diversity of labor functions considered in each study and variation in assumptions regarding staff qualifications, salary benefits, and working hours made comparisons difficult.

Each of the reviewed studies accounted for all the costs associated with a complete sequencing procedure. Costs for sample preparation, bioinformatics, reporting, and data storage were included in addition to those directly associated with the sequencing step. Clinical interpretation of variants, in particular, has been considered as an important cost associated with genome-wide sequencing,[12] and therefore, excluding it from cost estimates may increase risk of bias.[29] Discount rates considered for the analysis along with the year and currency of the unit costs were also reported in most of the papers. However, not every study provided detailed justifications for the selection of discount rates[24] or explained if their costs had been adjusted for inflation,[22] which limits reporting transparency.[16,25] Nonetheless, most of the studies provided clear sample sizes used for estimations, and when assumptions about sample numbers were made, including total institutional capacity[26] or historical sequencing throughput,[22-25,27,28] a justification was provided. A well-defined scope of inputs for a cost estimation decreases the risk of bias from exclusion of important cost items, which has been described as a common limitation in cost estimations.[29]

The potential lack of generalizability outside of the setting or population being evaluated is a well-known limitation of microcosting.[30] Input parameters may vary between institutions because of the negotiations over the costs of equipment supply and maintenance contracts. In addition, costs calculated in research settings may consider actions necessary to guarantee guideline adherence and other research procedures that do not reflect clinical practice.[29,30] Conversely, clinical laboratories need to comply with diagnostic laboratory standards, which is an additional cost over research laboratories. Cost and volume uncertainty can be directly incorporated into the point estimates when using a probabilistic approach to microcosting that models range for each cost item to reflect variation across institutions.[13] This method also makes it possible to calculate CIs around cost estimates for use in decision-making. Most of the studies included in this review followed the general recommendations for generalizability of results, including considerations for the application of the estimation methods in other settings[13,29] and reporting estimates in both local currency and US dollars, accounting for inflation and conversion rates. Characterizing parameter uncertainty from model inputs is of relevance in economic evaluations for health technology assessment, which can have an effect on the decision of national funding bodies to recommend a new technology.[9]

The variation in resource use and cost estimates is observed in the studies reviewed is possibly explained by the methodological differences across studies. For instance, the variation in workflow steps stems from the use of different sequencing platforms, which have variations in throughput levels, run times, or sample processing requirements.[16] However, sequencing workflows and therefore costs are expected to change when new methods are developed or when higher throughput equipment is used.[15,16,22,31] A few authors[16,30] have highlighted the value of disaggregating costs for medical interventions, in which technology, and therefore costs, are rapidly evolving. Observing these patterns and predicting changes in the future are essential for allocating resources for health care and creating a sustainable health care budget, especially in light of the rapid advance of genomic technologies.[16,31] Future costing studies should therefore aim to report costs in a more comprehensive fashion, which would enable comparisons across studies and provide insights into the economic cost and associated uncertainty in the resources required for the delivery of genomic sequencing.

Our findings can guide future costing analyses of ES and GS, allowing researchers to strengthen their methodologies to generate robust and generalizable cost estimates and to provide more accurate cost-effectiveness estimates to inform decision-making priorities. More accurate and generalizable estimates of the cost of delivering genomic testing will provide greater certainty on the budget impact associated with the implementation of genomics.[11,13,15] Most of the estimates for ES/GS testing for rare diseases identified by this review are well above the currently reimbursed amounts for genomic testing for monogenic disorders by the Australian Medical Benefits Schedule (MBS) of $1404 (AU$2100) for singleton (MBS item 73358) and $1939 (AU$2900) for trio sequencing (MBS item 73359). The implications of these differences can lead to challenges for diagnostic laboratories to deliver the test at the benefit price and create out-of-pocket expenses for patients.

This systematic review presents certain limitations. Although the search strategy was informed by published literature and developed in consultation with a research

librarian, it used targeted keywords and may have missed studies that were not explicitly labeled as microcosting or bottom-up costing studies. Nonetheless, reference checking of included studies is likely to have limited such omissions, which are unlikely to have significantly altered the conclusions drawn in this review because of the limited number of published microcosting studies of genomic sequencing.[5,10,16] Furthermore, to the best of our knowledge, no framework to objectively assess the methodological quality and reporting of microcosting studies currently exists. Therefore, critical appraisal tools for economics evaluations, such as Consolidated Health Economic Evaluation Reporting Standards 2022,[32] could not be employed to assess the quality of the methods to measure resource use and unit costs to estimate delivery costs from the included studies. To account for this, the reporting clarity and comprehensiveness of the microcosting methodologies were evaluated, presenting recommendations drawn from publications using microcosting for health interventions and genomic sequencing of common conditions[13,14,16,30] and costing guidelines in global health.[29]

Given the value of microcosting to formulate accurate cost estimations for new interventions, future research studies will need to standardize the procedures and tools for developing and reporting microcosting analyses. This will have a positive effect on the quality and transparency of studies and data reliability for decision-making. To this end, the microcost model template as part of the Genomic Sequencing Procedures Pricing Project from the Association for Molecular Pathology[23] might be a useful starting point for standardizing costing procedures.

Finally, this review was limited to the use of ES and GS for diagnosis of cancer and rare diseases. Despite the improved health outcomes and greater benefits achieved by these techniques, the diagnostic challenges of ES and GS, such as uninformative test outcomes in around 50% of cases, have been highlighted in the literature.[2,21] Future studies should consider the costing of additional approaches such as reanalysis of existing data and the use of functional genomic tests (such as transcriptomics and proteomics), which have both been demonstrated to improve diagnostic outcomes. Functional genomics studies have proved useful in the identification of novel therapeutic targets, gene discovery, and assessment of phenotypic heterogeneity and overlapping in rare disease patients.[2,21]

This article provides key insights on the methodological approaches to estimate the cost of ES and GS for the diagnosis of rare diseases and cancer. It highlights the importance of developing generalizable and comparable costing methodologies based on local data that reflect the various stakeholder perspectives and costs involved in the adoption of genomic sequencing in the health care system. The methods for the accurate estimation of costs of genomic sequencing for rare diseases presented in this article will be valuable in this context, assisting to lay the evidence foundations on the cost-effectiveness of integrating genomic technologies into the health care systems.

Data Availability

All relevant data are listed within the paper and its supporting information files.

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Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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References

1. Belsey J, Chaihorsky L, Chediak L, Currie G, Goranitis I, Marshall D. Global data access for solving rare disease. A health economics value framework. World Economic Forum; 2020. Accessed July 11, 2022. https://www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdf

2. Kerr K, McAneney H, Smyth LJ, Bailie C, McKee S, McKnight AJ. A scoping review and proposed workflow for multi-omic rare disease research. *Orphanet J Rare Dis*. 2020;15(1):107. http://doi.org/10.1186/s13023-020-01376-x
3. Cohen E, Berry JG, Camacho X, Anderson G, Wodchis W, Guttmann A. Patterns and costs of health care use of children with medical complexity. *Pediatrics*. 2012;130(6):e1463-e1470. http://doi.org/10.1542/peds.2012-0175
4. Tisdale A, Cutillo CM, Nathan R, et al. The IDeaS initiative: pilot study to assess the impact of rare diseases on patients and healthcare systems. *Orphanet J Rare Dis*. 2021;16(1):429. http://doi.org/10.1186/s13023-021-02061-3
5. Payne K, Gavan SP, Wright SJ, Thompson AJ. Cost-effectiveness analyses of genetic and genomic diagnostic tests. *Nat Rev Genet*. 2018;19(4):235-246. http://doi.org/10.1038/nrg.2017.108
6. Goranitis I, Best S, Christodoulou J, Stark Z, Boughtwood T. The personal utility and uptake of genomic sequencing in pediatric and adult conditions: eliciting societal preferences with three discrete choice experiments. *Genet Med*. 2020;22(8):1311-1319. http://doi.org/10.1038/s41436-020-0809-2
7. Kohler JN, Turbitt E, Biesecker BB. Personal utility in genomic testing: a systematic literature review. *Eur J Hum Genet*. 2017;25(6):662-668. http://doi.org/10.1038/ejhg.2017.10
8. Best S, Stark Z, Phillips P, et al. Clinical genomic testing: what matters to key stakeholders? *Eur J Hum Genet*. 2020;28(7):866-873. http://doi.org/10.1038/s41431-020-0576-1
9. Regier DA, Veenstra DL, Basu A, Carlson JJ. Demand for precision medicine: a discrete-choice experiment and external validation study. *Pharmacoeconomics*. 2020;38(1):57-68. http://doi.org/10.1007/s40273-019-00834-0
10. Fahr P, Buchanan J, Wordsworth S. A review of health economic studies comparing traditional and massively parallel sequencing diagnostic pathways for suspected genetic disorders. *Pharmacoeconomics*. 2020;38(2):143-158. http://doi.org/10.1007/s40273-019-00856-8
11. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med*. 2018;20(10):1122-1130. http://doi.org/10.1038/gim.2017.247
12. Mardis ER. The $1,000 genome, the $100,000 analysis? *Genome Med*. 2010;2(11):84. http://doi.org/10.1186/gm205
13. Jegathisawaran J, Tsiplova K, Hayeems R, Ungar WJ. Determining accurate costs for genomic sequencing technologies-a necessary prerequisite. *J Community Genet*. 2020;11(2):235-238. http://doi.org/10.1007/s12687-019-00442-7
14. Tsiplova K, Zur RM, Marshall CR, et al. A microcosting and cost-consequence analysis of clinical genomic testing strategies in autism spectrum disorder. *Genet Med*. 2017;19(11):1268-1275. http://doi.org/10.1038/gim.2017.47
15. Grosse SD, Gudgeon JM. Cost or price of sequencing? Implications for economic evaluations in genomic medicine. *Genet Med*. 2021;23(10):1833-1835. http://doi.org/10.1038/s41436-021-01223-9
16. Johnson K, Saylor KW, Guynn I, Hicklin K, Berg JS, Lich KH. A systematic review of the methodological quality of economic evaluations in genetic screening and testing for monogenic disorders. *Genet Med*. 2022;24(2):262-288. Published correction appears in *Genet Med*. 2022;24(4):969. https://doi.org/10.1016/j.gim.2021.10.008.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. http://doi.org/10.1136/bmj.b2535
18. McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV, Thomas J. Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3. Cochrane; 2022:33-65.
19. Xu X, Grossetta Nardini HK, Ruger JP. Micro-costing studies in the health and medical literature: protocol for a systematic review. *Syst Rev*. 2014;3:47. http://doi.org/10.1186/2046-4053-3-47
20. Griffith GL, Tudor-Edwards R, Gray J, et al. A micro costing of NHS cancer genetic services. *Br J Cancer*. 2005;92(1):60-71. http://doi.org/10.1038/sj.bjc.6602270
21. Hartley T, Lemire G, Kernohan KD, Howley HE, Adams DR, Boycott KM. New diagnostic approaches for undiagnosed rare genetic diseases. *Annu Rev Genomics Hum Genet*. 2020;21:351-372. http://doi.org/10.1146/annurev-genom-083118-015345
22. Bayle A, Droin N, Besse B, et al. Whole exome sequencing in molecular diagnostics of cancer decreases over time: evidence from a cost analysis in the French setting. *Eur J Health Econ*. 2021;22(6):855-864. http://doi.org/10.1007/s10198-021-01293-1
23. Pasmans CTB, Tops BBJ, Steeghs EMP, et al. Micro-costing diagnostics in oncology: from single-gene testing to whole- genome sequencing. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21(3):413-414. http://doi.org/10.1080/14737167.2021.1917385
24. Schwarze K, Buchanan J, Fermont JM, et al. The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom. *Genet Med*. 2020;22(1):85-94. http://doi.org/10.1038/s41436-019-0618-7
25. van Nimwegen KJM, van Soest RA, Veltman JA, et al. Is the $1000 genome as near as we think? A cost analysis of next-generation sequencing. *Clin Chem*. 2016;62(11):1458-1464. http://doi.org/10.1373/clinchem.2016.258632
26. Jegathisawaran J, Tsiplova K, Hayeems RZ, et al. Trio genome sequencing for developmental delay and pediatric heart conditions: a comparative microcost analysis. *Genet Med*. 2022;24(5):1027-1036. http://doi.org/10.1016/j.gim.2022.01.020
27. Gordon LG, White NM, Elliott TM, et al. Estimating the costs of genomic sequencing in cancer control. *BMC Health Serv Res*. 2020;20(1):492. http://doi.org/10.1186/s12913-020-05318-y
28. Sabatini LM, Mathews C, Ptak D, et al. Genomic sequencing procedure microcosting analysis and health economic cost-impact analysis: a report of the association for molecular pathology. *J Mol Diagn*. 2016;18(3):319-328. http://doi.org/10.1016/j.jmoldx.2015.11.010
29. Vassall A, Sweeney S, Kahn JG, et al. Reference case for estimating the costs of global health services and interventions. Global Health Cost Consortium. Updated September 12, 2017. Accessed July 19, 2022. https://ghcosting.org/pages/standards/reference_case
30. McCutchan PK, Yates BT, Jobes DA, Kerbrat AH, Comtois KA. Costs, benefits, and cost-benefit of Collaborative Assessment and Management of Suicidality versus enhanced treatment as usual. *PLoS One*. 2022;17(2):e0262592. http://doi.org/10.1371/journal.pone.0262592
31. Weymann D, Laskin J, Roscoe R, et al. The cost and cost trajectory of whole-genome analysis guiding treatment of patients with advanced cancers. *Mol Genet Genomic Med*. 2017;5(3):251-260. http://doi.org/10.1002/mgg3.281
32. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 explanation and elaboration: a report of the ISPOR CHEERS II Good Practices Task Force. *Value Health*. 2022;25(1):10-31. Published correction appears in *Value Health*. 2022;25(6):1060. https://doi.org/10.1016/j.jval.2021.10.008.