

Costing strategies for genomic diagnostic interventions in rare diseases: A scoping review protocol

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ABSTRACT: The ability to diagnose rare diseases has increased with the recent development of genomic technologies. Their complexity and high cost create barriers to broader dissemination. Cost-related information is crucial for wider adoption. This study aims to map and synthesize the costing methodologies used in economic evaluations of genomic technologies applied to rare disease diagnosis and to identify the most relevant cost items. The presented protocol seeks to document the processes involved in planning and conducting the methodological review, which will follow the Joanna Briggs Institute guidelines. The PCC framework (Population, Concept, Context) will systematize the search for published studies in the MEDLINE, Embase, LILACS, Web of Science, Scopus, and NHS Economic Evaluation databases, covering January 2000 to December 2024. Two independent reviewers will select articles in two phases (title/abstract screening followed by full-text assessment), applying predefined inclusion and exclusion criteria, with disagreements resolved by a third reviewer. Results will be analyzed according to genomic technologies and costing methodologies, and presented as narrative summaries, figures, tables, and flowcharts. The synthesis may contribute to the design of cost studies and economic evaluations of these technologies in Brazil.

Keywords: Rare diseases. Diagnostic genomic technologies. Costs and cost analysis.

Estratégias de custeio de intervenções diagnósticas genômicas nas doenças raras: protocolo de revisão de escopo

RESUMO: A capacidade de diagnosticar doenças raras tem se elevado com o desenvolvimento recente das tecnologias genômicas. Sua complexidade e alto custo agregam barreiras para sua disseminação mais ampla. Informações de custo são cruciais para sua maior adoção. Este estudo objetiva mapear e sintetizar as metodologias de custeio utilizadas nas avaliações de custo das tecnologias genômicas empregadas no diagnóstico das doenças raras e identificar os itens de custo mais relevantes. O protocolo apresentado visa documentar os processos envolvidos no planejamento e condução metodológica da revisão, que será realizada conforme as diretrizes do Instituto Joanna Briggs. A estratégia PCC

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(população, conceito e contexto) sistematizará a pesquisa de estudos publicados nas bases de dados MEDLINE, Embase, LILACS, Web of Science, Scopus e NHS Economic Evaluation, de janeiro/2000 a dezembro/2024. Dois revisores independentes selecionarão os artigos em duas fases (título e resumo, seguido da avaliação do texto completo), adotando critérios de inclusão e exclusão pré-definidos, com discordâncias resolvidas por um terceiro revisor. Os resultados serão analisados segundo as tecnologias genômicas e as metodologias de custeio, e apresentados em formato de resumos narrativos, figuras, tabelas e fluxogramas. A síntese obtida pode contribuir no desenho de estudos de custo e avaliações econômicas das tecnologias no Brasil.

Palavras-chave: Doenças raras. Tecnologias genômicas diagnósticas. Custos e Análise de Custo.

Introduction

The genome determines the cause of disorders that affect millions of people around the world and, depending on the environment, puts individuals at greater risk of cardiovascular disease, cancer, and several other diseases (WORLD HEALTH ORGANIZATION, 2000). Genomics is the study of the complete genetic material of organisms and how genes and other genetic elements operate and interact with each other and the environment (PAN AMERICAN HEALTH ORGANIZATION, 2024).

Human genome sequencing revolutionized our understanding of the role of genetic inheritance in health and disease. The use of genomics in medicine, public health, and other fields has increased dramatically in the 25 years since the first complete sequencing of a human genome. Since then, genetic assessment and testing have been employed in several medical disciplines to assist in diagnosing, treating, prognosis, and ongoing management of diseases in children and adults, with applications in oncology, neurology, and rare diseases (WORLD HEALTH ORGANIZATION, 2022). The latter is the condition of interest in the review proposed here.

Rare diseases (RD) correspond to a heterogeneous set of clinical conditions that affect up to 65 people in every 100 thousand individuals or 1.3 for every 2 thousand people (BRASIL, 2014). In the European Union, a rare disease affects fewer than 5 in 10,000 people; in the United States, it affects fewer than 200,000 people nationwide (or 7.5/10,000 inhabitants). Although the precise definition varies between jurisdictions regarding frequency and other defining characteristics 5, a key aspect systematically found in rare diseases is the relatively low incidence/prevalence (ORPHANET, 2025).

Some 3.5 to 5.9% of individuals worldwide are estimated to have a rare disease. These diseases comprise approximately 7,000 different conditions, which has increased with the improvements and expansion of multiomics technologies. More than 70% of these diseases are of genetic origin, and 69.9% have onset in the pediatric period (NGUENGANG WAKAP et al., 2020). Although the individual prevalence of a specific genetic disorder may be low, the global impact of rare diseases can be significant for families and health systems regarding mortality, morbidity, and economic burden on the

health system (ANGELIS; TORDRUP; KANAVOS, 2015; WORLD ECONOMIC FORUM, 2020). The total economic burden of these diseases in the United States was estimated at \$966 billion in 2019, of which 43% (\$418 billion) would be direct medical costs (GONZALUDO et al., 2019).

The prolonged delay between symptom onset and diagnosis of a rare disease is well documented in the literature (ANDERSON; ELLIOTT; ZURYNSKI, 2013; TEUTSCH et al., 2023). It is estimated that up to 50% of patients with a rare genetic disease never receive a diagnosis, and many are subjected to a diagnostic odyssey that includes recurring appointments with specialists and multiple laboratory, imaging, and genetic diagnostic procedures (SHASHI et al., 2014). The average time to diagnose a rare genetic disease using genetic, cytogenetic, and genomic testing currently ranges from 4.8 to 7.4 years, costing health systems more than US\$5,000 per patient in laboratory testing alone (WEYMANN et al., 2024). The lack of or delay in diagnosing these diseases results in significant costs (DRAGOJLOVIC et al., 2020; TAN et al., 2017).

As 80% of rare diseases are genetic, genomics has played an increasing role in diagnosing and treating such diseases (ADAMS; ENG, 2018; VINKŠEL et al., 2021). Its use enables more timely molecular diagnosis, reducing the diagnostic journey. It improves disease management, including targeted treatments and surveillance for late-onset comorbidities, and informs genetic counseling regarding recurrence risks and prenatal diagnostic options for families (FERNANDEZ-MARMIESSE; GOUVEIA; COUCE, 2018; SAWYER et al., 2016).

Genomic techniques' acceptance and widespread use have accelerated with the development of next-generation sequencing (NGS) technologies. While whole-exome sequencing (WES) analyzes protein-coding sections of the genome and represents 1-2% of the total genome, whole-genome sequencing (WGS) analyzes both coding and non-coding regions. Subsequent techniques and process throughput improvements have reduced costs and made sequencing more accessible (GIANI et al., 2020; SATAM et al., 2023). However, these are still complex and expensive technologies, which vary with the genomic technique used, the clinical condition, and the context in which diagnostic technology is employed. This is expressed in a still highly variable availability of financing by several health systems (PHILLIPS et al., 2021).

Rising healthcare costs in health systems have stimulated a growing interest in studying healthcare interventions' cost and cost-benefit relationships. Cost estimates are the basis for any economic evaluation and should be thoroughly assessed to inform efficient resource allocation, which also applies to omics diagnostic technologies. In this context, examining the costs of genomic applications for conducting evaluations and adoption in healthcare practice is crucial.

Economic evaluations compare costs and outcomes of two or more alternatives under examination (e.g., diagnostic strategies), and they must explain how the cost information was obtained.

However, existing guidelines for economic evaluations often do not provide sufficient detail for the methods and techniques to be used when conducting costing analyses, which can substantially impact cost estimates (BARNETT, 2009; MOGYOROSY; SMITH, 2005; XU; GROSSETTA NARDINI; RUGER, 2014).

Although accurately defining the costs of various genomic technologies is mandatory (GORDON et al., 2020; JEGATHISAWARAN et al., 2020), it involves many challenges due to the inherent complexity of the sequencing process, which includes different steps in the sequencing workflow, hindering the definition of a standard sequencing procedure. There is also considerable uncertainty about which costs of genomic technologies should be collected and when they should be collected. Furthermore, the costs of these technologies vary significantly between laboratories and countries, and over time, as technologies advance in technical terms (BUCHANAN; WORDSWORTH; SCHUH, 2013).

As a result of these different aspects, reviews of genome sequencing economic evaluations have pointed out the need to improve the methodologies' rigor and for greater transparency regarding the data and items included in the cost estimates of these diagnostic approaches to generate robust economic evidence (ALAM; SCHOFIELD, 2018; BOUTTELL et al., 2022; PAYNE et al., 2018).

Although numerous reviews are related to the economic evaluation of genetic sequencing technologies (ALAM; SCHOFIELD, 2018; FAHR; BUCHANAN; WORDSWORTH, 2020; REZAPOUR et al., 2023; SCHWARZE et al., 2018), synthesis studies on these technologies' cost strategies are much scarcer and not always targeted at rare diseases. A systematic literature review was conducted to identify studies that used microcosting methods to estimate the cost of genomic sequencing in diagnosing cancer and rare diseases in research or clinical practice settings. Search in the databases was completed in March 2022 and restricted to publications in English. Four of seven studies published between 2016 and 2022 examined the costs of exome sequencing and whole genome sequencing in rare diseases, one exclusively in a research setting. The authors concluded that there were significant differences in the steps of the sequencing workflow process and the level of detail of the steps and resources employed, limiting comparisons between studies (SANTOS GONZALEZ et al., 2023).

Systematic or scoping review protocols focusing on the costing strategies of the selected technologies were not identified in the PROSPERO and Open Science Framework databases or in a literature search conducted in Medline (via PubMed). This absence and the findings of the aforementioned review of Santos Gonzalez et al. (2023) motivated the development of the proposed scoping review.

The scoping review will systematize the main costing methods used to evaluate genomic technologies for diagnosing rare diseases, identifying the cost components with the most significant

impact on estimated costs and the gaps in the current application of cost analyses.

Methods

Study design

This protocol describes the methodological framework steps for conducting a scoping review of studies addressing the cost of genomic technologies in diagnosing rare diseases. It was structured based on the 2015 Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist (SHAMSEER et al., 2015) and aims to reduce biases while searching for and selecting studies and extracting data, adopting transparent and standardized selection criteria.

Scoping reviews are used when one wishes to map the existing literature in a given field regarding its nature, characteristics, key concepts, and volume (ARKSEY; O'MALLEY, 2005). This type of review is justified by the scope of the research question and its more exploratory nature, aiming to capture the largest contingent of studies related to the topic, besides the expected existence of studies with diverse methodological designs (COLQUHOUN et al., 2014).

The review will be conducted according to the Joanna Briggs Institute (JBI) methods for scoping reviews and will involve the following steps: (i) Defining the research question; (ii) Establishing study eligibility criteria; (iii) Developing search strategies; (iv) Screening and selecting evidence; (v) Extracting data; and (vi) Analyzing and presenting results (AROMATARIS et al., 2024; PETERS et al., 2020).

This review protocol was structured based on the 2015 Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist (SHAMSEER et al., 2015). The protocol was registered in the Open Science Framework to ensure transparency (<https://doi.org/10.17605/OSF.IO/2DCUX>).

Objective/Research question

The research questions that will guide the investigation, analysis, and consolidation of evidence are:

- a) What costing methodologies have been used in cost assessments of genomic technologies in diagnosing rare diseases?
- b) What main cost components are involved, and which items have the most significant impact identified in the studies?

The research questions were structured using the PCC mnemonic (Population, Concept, and Context), which was recommended as an alternative to the population, intervention, comparator, and outcomes model in reviews without a well-defined clinical question (PETERS et al., 2020). The PCC

elements, shown in Table 1 below, will guide the search and refinement of the inclusion and exclusion criteria adopted in the scoping review.

Table 1. PCC mnemonic used in scoping review

Criteria	Description
Population	Individuals suspected or diagnosed with rare diseases
Concept	Diagnostic genomic technologies
Context	Costing studies and cost elements involved

Source: Prepared by the authors.

Eligibility criteria

Relevant studies will be selected using specific inclusion and exclusion criteria based on the components of the PCC mnemonic as set out below.

Inclusion criteria

The clinical application of diagnostic genomic technologies of interest refers to rare diseases, especially those of genetic origin.

Since there may be studies that focus on a disease with a specific name and considering that RD encompasses an extensive set of diseases, two complementary strategies were devised in this situation, which corresponds to checking the name in the manuscript in specific databases that gather information on rare diseases and orphan drugs: (a) Orphanet (available at <https://www.orpha.net/en/disease/list/e>) and (b) National Organization for Rare Disorders (NORD) (available at <https://rarediseases.org/rare-diseases/>). Both databases provide comprehensive lists of all rare diseases registered in their respective databases, are updated periodically, and allow alphabetical searching.

Studies that additionally include multiple different clinical applications of rare diseases (e.g., cancer) will be accepted if they detail separately the costs related to RD. However, only the information related to the latter will be subject to extraction.

Regarding diagnostic technologies, the review will focus specifically on whole-exome sequencing (WES) and whole-genome sequencing (WGS), as these are the newest next-generation sequencing technologies with potentially higher costs. There will be no restrictions on the type of biological sample, or the platforms used for analysis.

We aim to identify publications reporting data on test costs and the costing strategies employed in their estimates. Thus, both partial economic evaluations (cost studies) and complete economic evaluations (cost-effectiveness, cost-utility, or cost-benefit studies, as per definitions provided by Drummond et al. (DRUMMOND, 2015)). The costing method and cost items included must be detailed to include complete assessments. However, there will be no restrictions on the strategies under examination if they include WGS and WES, nor on the comparator (traditional diagnostics, single-gene

tests, or targeted panels).

Since one of the objectives of the review is to identify the costing strategies employed in the cost assessments of diagnostic genomic strategies, the accepted profile of the approaches employed will be broad regarding the level of disaggregation adopted in the identification and measurement of resources and cost components (micro-costing vs. gross costing or macro-costing) and the method for assessing resources and cost components (top-down vs. bottom-up) (DRUMMOND, 2015; ŠPACÍROVÁ et al., 2020). Figure 1 summarizes and provides concise descriptions of the costing methodologies that guided the studies' selection (and, subsequently, the data extraction) to be included in the review.

Figure 1. Classifications of costing methods of interest for the scoping review to be conducted

Level and type of data collected			
		Expenditure data collected at organisational level (e.g. cost centre) and then distributed to the activity units	Resources use data collected for each individual patient and then multiplied by unit cost to estimate the expenditure
Level of identification of resource use items	Highly detailed resource use items are identified	<i>Top-down micro-costing</i>	<i>Bottom-up micro-costing</i>
	Aggregate resource use items are identified	<i>Top-down gross-costing</i>	<i>Bottom-up gross-costing</i>

Source: Prepared by the authors based on Špacírová et al. (2020, p. 531) and Tan et al. (2009, p. 40).

Finally, regarding the research context, studies that evaluate the cost of selected genomic interventions for diagnostic purposes in any healthcare setting will be accepted.

Exclusion criteria

Commentaries, letters, abstracts, editorials, reports, economic models, conceptual articles, conference proceedings, academic dissertations and theses, literature reviews, and studies that did not evaluate the selected genomic techniques will be excluded. Studies published in languages other than English, Spanish, and Portuguese will be excluded but recorded to identify potential language biases. Articles that represent duplications of the same study will also be excluded.

Identifying relevant studies

The following databases will be used: MEDLINE (via PubMed), Embase, LILACS (via BVS), Scopus, and Web of Science. To maximize the number of potentially relevant studies identified, no

language restrictions will be applied in the search . The search will be limited to human studies published from 2000 to 2025. The choice of the initial year is based on the emergence of the first Next Generation Sequencing (NGS) platforms from the second half of the 2000s.

When available, the search strategies will use health descriptors (MeSH, DeCS, and Emtree) and search for specific free terms connected using the Boolean operators AND, OR, and NEAR, adapted for each database (Table 2).

Table 2. Descriptors and search terms used in the scoping review search strategies

Acronym element	DeCS	Mesh/Emtree	Key words
Population	Doenças raras	Rare Diseases	rare diseases* rare disorder* orphan diseases* extremely rare diseases* low-frequency disease very rare diseases* rare condition ultra-rare diseases* ultra-orphan diseases*
Concept	Genômica	Genomics	genomic diagnostic test* genome sequencing whole genome sequencing exome sequencing next generation sequencing WGS WES high-throughput nucleotide sequencing
Context)	Custos e análises de custo	Costs and Cost Analysis Economic evaluation	costs and cost analysis/methods cost method* costing method* cost* study cost* analysis microcost* micro-cost* macrocost* bottom-up cost* activity-based cost* (time-and-motion stud* time-and-motion analys* top-down cost*

Source: Prepared by the authors, 2025.

Initial MEDLINE searches were conducted (via OVID) on 28 January 2025; their results are shown in Table 3 below. The search strategies in the other databases are being developed collaboratively and iteratively by the reviewers with the support of a librarian.

Table 3. Search strategies and number of references generated in the MEDLINE database (via OVID)

Search	Search strategy	Number of references retrieved

1	(rare adj2 diseas*).ti,ab,kf.	53.634
2	(rare adj2 disorder*).ti,ab,kf.	28.542
3	(rare adj2 abnormal*).ti,ab,kf.	2.803
4	(ultra-orphan adj2 diseas*).ti,ab,kf.	35
5	(ultra-orphan adj2 disorder*).ti,ab,kf.	2
6	(ultra-orphan adj2 abnormal*).ti,ab,kf.	0
7	rare condition.ti,ab,kf.	23.510
8	(ultra-rare adj2 diseas*).ti,ab,kf.	281
9	(ultra-rare adj2 disorder*).ti,ab,kf.	185
10	(ultra-rare adj2 abnormal*).ti,ab,kf.	0
11	(low-frequency adj2 diseas*).ti,ab,kf.	101
12	(low-frequency adj2 disorder*).ti,ab,kf.	35
13	(low-frequency adj2 abnormal*).ti,ab,kf.	102
14	or/1-13	106.183
15	Genomics/	73.484
16	Genomic*.ti,ab,kf.	409.157
17	(Genom* adj3 (diagnos* or test)).ti,ab,kf.	3.773
18	((Genom* or exome or "next Generation" or Nucleotide) adj2 sequenc*).ti,ab,kf.	288.359
19	WGS.ti,ab,kf.	10.099
20	WES.ti,ab,kf.	8.199
21	or/15-20	630.048
22	Economics/	27.544
23	Economics, Nursing/	4.013
24	Economics, Medical/	9.299
25	Economics, Pharmaceutical/	3.154
26	exp Economics, Hospital/	26.097
27	Economics, Dental/	1.922
28	exp "Fees and Charges"/	31.605
29	exp Budgets/	14.312
30	budget*.ti,ab,kf.	39.589
31	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	307.999
32	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	9.047
33	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	240.663
34	(value adj2 (money or monetary)).ti,ab,kf.	3.370
35	exp models, economic/	16.690
36	economic model*.ab,kf.	4.650
37	markov chains/	16.781
38	monte carlo method/	33.742
39	monte carlo.ti,ab,kf.	65.675
40	exp Decision Theory/	14.061

41	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	47.543
42	or/22-41	697.686
43	(microcost* or micro-cost* or (Bottom-up adj2 cost*) or "time-and-motion").mp. or (top-down adj2 cost*).ti,ab,kf.	9.249
44	42 or 43	704.817
45	14 and 21 and 44	140

Note: Search conducted on January 28, 2025.

Source: Prepared by the authors, 2025.

Whenever possible, alerts will be set up in bibliographic databases to receive notifications of the publication of new articles after the search date. These alerts will be updated at the end of the search process and before the end of the selection phase to ensure the inclusion of new studies.

In addition, studies will also be searched in gray literature using two databases related to health technology assessment (HTA), which provide studies and technical reports carried out by international HTA agencies. One is the basis of the International Network of Agencies for Health Technology Assessment (INAHTA) through the electronic address <https://database.inahta.org/>. The other is the NHS Economic Evaluation Database (NHS EED), organized by the Centre for Reviews and Dissemination and the University of York (<https://www.crd.york.ac.uk/CRDWeb/>), which is specific to economic studies. In both cases, the search will be guided by MeSH terms and keywords corresponding to the elements of the PCC acronym without language restriction.

Additional references will be searched through cross-search in the reference lists of literature reviews and the studies included in the review, seeking to identify other potential articles related to the theme and increase the research coverage.

References identified in the searches will be entered into the Zotero open-access bibliographic citation management *software* (<https://www.zotero.org/>) to identify and remove duplicate references.

Study selection

Two independent researchers will conduct two stages of article selection after removing duplicates. A third reviewer will resolve any disagreements.

In the first screening stage, titles and abstracts will be assessed to determine whether they meet the above inclusion criteria. In the second stage, the full versions of the articles, including those for which the title and abstract do not indicate whether they meet the inclusion criteria, will be examined to determine whether they meet the eligibility criteria.

Separate forms containing detailed instructions will be developed in Google Forms to standardize and document the two stages of the study selection process. Reasons for studies' exclusion after full-text review will also be documented.

The study selection process, including the number of articles retrieved in the search, duplicates

excluded, articles selected, and finally, those included in the scoping review, will be summarized using the PRISMA flowchart (PAGE et al., 2021).

Methodological quality assessment

Although there is debate in the literature about the mandatory inclusion of the assessment of the methodological quality of studies in scoping reviews (KHALIL et al., 2016), This review aims to summarize the cost studies' quality aspects.

In the absence of a specific quality assessment tool for costing studies, a modified version of the Consensus on Health Economic Criteria Checklist (CHEC) tool (EVERS et al., 2005) will be adopted to evaluate the quality of the included studies.

The CHEC checklist represents a generic core set of 19 items that can be used to assess the methodological quality of economic evaluations. However, several items are not suited to the intended purpose of this scoping review and will not be included in the analysis (item 5 – selected time horizon's appropriateness; items 10–12 – outcome assessment quality; item 14 – appropriate discounting of future costs and outcomes). Items 7–9, which assess the level to which all relevant costs have been adequately identified, measured, and valued, will be the review's focus and considered in detail.

The methodological quality assessment will follow the standard of analysis by two separate reviewers, with discrepancies resolved by discussion with a senior reviewer.

Data extraction

Two independent reviewers will also conduct this phase, with a third reviewer mediating any disagreement using the selected articles' full text and supplementary materials.

Extracted data will be collected using a standardized electronic data collection form developed in Google Forms. The form will be pre-tested on a set of studies included in the review to determine whether the content and format are consistent with the research question and the purpose of the review and to promote changes, if necessary.

The authors of the selected studies may be contacted for clarification or to request additional data from the corresponding e-mail addresses for a maximum of two attempts. The following information is initially expected to be extracted:

- a) Study identification data – a unique identifier, title, journal, and year of publication.
- b) Study characteristics – study country, research funding source, study purpose, number of participating centers (single site, multiple centers), rare disease addressed, genomic technology examined, study locus and context (research, clinical practice, hospital, laboratory), sample size studied and number of tests, cost data collection time (prospective, retrospective, both).

- c) Costing study-related aspects – the type of economic evaluation conducted (descriptive cost study, comparative cost analysis, full economic evaluation/type of EA); descriptive or comparative), the approach used for costing (micro-costing/macro-costing; top-down/bottom-up); unit of analysis (cost per sample tested, cost per case, and the like), data collection year/period; reference year and currency of costs;
- d) Information on cost components (human resources involved in preparing biological materials and performing tests; equipment; supplies and consumables for preparing biological materials and performing tests; data storage-related costs; administrative/overhead costs, and the like) and resource items cost; details of how resources were measured (e.g., interviews; direct observation, time and motion studies, electronic databases) and valued (e.g., invoice amounts; hospital human resources department; provider price lists); total cost per test and cost component, and any cost drivers identified by the authors with full details of the cost drivers reported.
- e) Aspects related to assessing methodological quality using the CHEC instrument (EVERS et al., 2005) to be modified to suit the research objectives.

Analysis and presentation of the results

The data collected in the Google Forms form will be exported and analyzed using Excel® software. Results will be tabulated considering the genomic technologies examined and costing methodologies and presented in a descriptive format using narrative summaries, figures, tables, and flowcharts. Cost results from trials will not be combined into summary measures.

The final review report will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Scoping Reviews (PRISMA-ScR) instrument (TRICCO et al., 2018).

Ethical aspects

This protocol refers to a coping review, with published scientific studies or public documents with unrestricted access as sources of information, dispensing with previous ethical approval by human research ethics committees. The authors declare that they have no ties to the industry producing the technologies subject to review or to funding institutions that could characterize potential conflicts of interest, and their results will be published in an open-access journal or presented at relevant scientific events.

Final considerations

The rigor and reliability of a review are based on prior planning and documentation of the methodology used in its execution. It increases transparency because it allows others to compare the protocol and the review after its completion, identifying changes that have occurred and selective

reporting. It also allows for the minimization of arbitrary decisions regarding study selection and data extraction. Thus, the protocol for conducting the proposed scoping review aimed to systematize the succession of methodological approaches classically established in the literature, serving as a guide for the researchers involved.

Considering the scarcity of the literature, the findings compiled from this review are expected to provide a comprehensive and updated overview of the costing methodologies adopted to examine the costs of diagnostic genomic interventions in rare diseases.

Furthermore, the synthesis to be presented may contribute to the design and implementation of cost studies for these technologies in the Brazilian scenario, which have not yet been incorporated into the Brazilian Unified Health System or are not widely available in the national health services network. Its results may support the future development of comprehensive economic evaluation studies, which are essential for increasing the efficiency of the national health system. Finally, they may assist service providers who wish to plan the provision of such diagnostic technologies and may also support the definition of reimbursement amounts to be paid by the SUS, should they decide to introduce them at some point in the Brazilian public system.

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