The Cost of Hereditary Pediatric Cataract’s Clinical and Genetic Diagnosis With Whole Exome Sequencing From a Middle-income Country Perspective: Can We See Any Gains?

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Abstract

Up to 25% of pediatric cataract cases are inherited. There is scarce information in the literature regarding the cost of whole exome sequencing (WES) for hereditary pediatric cataract. Molecular diagnosis of hereditary pediatric cataract is important for a comprehensive genetic counseling. We performed a partial economic evaluation using a microcosting approach with a bottom-up technique to estimate the cost of clinical and genetic diagnosis using WES for hereditary pediatric cataract under the Brazilian governmental healthcare system's perspective. One hundred and ten participants from twenty-nine families from Rio de Janeiro city (RJ) were included. Direct costs of consumables, staff and equipment were used. Two scenarios were created: 1. Reference scenario included patients with hereditary pediatric cataract plus two family members in RJ. 2. Alternative scenario considered other genetic diseases resulting in 5,280 exams per month. Sensitivity analysis was performed. In the reference scenario the total cost per exam (clinical and genetic) was 609.51 United State Dollars (USD) and in the alternative scenario it was 541.20 USD. Considering only WES, its cost per exam was 455.29 USD in the reference and 386.98USD in the alternative scenarios. Sensitivity analysis showed that the most important costs were consumables in both scenarios. Economic evaluations can help inform policy decisions specially in middle-income countries such as Brazil.

Introduction

Currently, there are 503 genes associated with pediatric cataracts (1). Identifying the molecular causes of pediatric cataracts is important because between 8.3 and 25% of them are believed to be inherited and 15% are associated with a systemic disease, where the eye can be a sentinel organ (2).

Recent advances in the field of genomics have revolutionized molecular diagnosis of genetic disorders, resulting in a better understanding of their pathophysiology, reduction of the diagnostic odyssey, and enablement of the development of potential therapies and personalized familial counseling (3, 4).

Whole exome sequencing (WES) is a comprehensive test recommended for genetic diseases with a significant overlap in clinical presentation or when there are many potential genes related to a clinical presentation. Health systems in countries such as France and the United Kingdom perform WES for many health diseases (5, 6). These countries have a national healthcare system similar to Brazil's, where exome sequencing is only available in the governmental healthcare system for a few diseases and in specific genetic reference services.

Ten years ago, the World Health Organization recommended measures to implement DNA-based diagnosis in low and middle-income countries to enhance their expertise in genomics (7). Some of these recommendations are training services, public education, developing bioinformatics and bioethics formation, in addition to promotion of research resources allocation (4, 7).

Despite these efforts, an enormous gap between low-middle and high-income countries still remains. For instance, less than 10% of genetic laboratories registered by the Genetic Testing Registry are settled in middle-income countries while more than 90% are in high-income countries (8). One major obstacle is presumed to be its cost considering a middle-income country scenario (9).

Technical performance and clinical indication of genetic testing have been extensively discussed in the literature, but economic evaluation has emerged as a fundamental information for multidisciplinary decision-making in health (10). Estimating the cost of a new technology can define its affordability and aid policy-makers to allocate scarce healthcare funds, especially in low and middle-income countries.

In 2020, the Brazilian government launched the National Genomic Program to embed precision medicine in our public healthcare system. The main objective was to create a genomic national data with 100,000 Brazilian genomes including rare diseases, cardiopathies, cancers and infectious diseases (11).

The purpose of this study was to perform a cost estimation of clinical and genetic diagnosis with WES for hereditary pediatric cataracts through the perspective of the Brazilian national healthcare system.

Material and Methods

1. Context

Brazil is a middle-income country with a large and publicly funded healthcare system (SUS) that is universally available and used by more than 70% of its population (12). There are 27 reference centers for the management of patients with rare diseases in the country and Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira (IFF) in Rio de Janeiro, is one of them. It is estimated that only 30% of the needs for evaluation of patients with rare diseases are met (13). Patients with eye diseases are managed in ophthalmic centers and those with suspected genetic etiology are to be referred to rare disease reference centers which represent a bottleneck towards the final diagnosis. In this scenario, the government pays up to 620 USD per year for the management (diagnosis, treatment, rehabilitation) of a patient with any rare disease.
The Instituto Nacional do Coração (INC) in Rio de Janeiro has an ongoing national research project for the diagnosis of hereditary cardiovascular diseases (The Brazilian National Network of Cardiovascular Genomics) (14) and, in addition, also performs molecular diagnosis of other genetic diseases. Both INC and IFF established a partnership for testing genetic diseases.

2. Study design and perspective

This is a partial economic evaluation for unit cost estimation of hereditary pediatric cataract diagnosis (clinical and genetic) through the SUS' perspective. We performed a microcosting approach with a bottom-up technique. This approach was used because the procedure for ocular diseases is not currently available in the clinical practice by SUS and that is the first step for other economic evaluations. The cost estimation was developed in an Excel 365 software (Microsoft, USA).

3. Population and setting

This study is part of the project CATBRA: A Brazilian approach for genomic evaluation of familial pediatric cataract patients that aims to identify variants associated with familial pediatric cataract and to analyze its impact in the management of these patients and families. The eligible population included one hundred and ten participants selected from twenty-nine different families within a cohort of pediatric cataract patients from a non-profitable health organization dedicated to the management (diagnosis, treatment and follow-up) of pediatric cataract in Rio de Janeiro, Brazil. Inclusion criteria encompassed patients up to 18 years old with a history of pediatric familiar cataract. Exclusion criteria included history of congenital TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, varicella zoster, zika), and the use of corticosteroids or ocular trauma. We assumed pediatric cataract as congenital cataract or acquired during infancy. Clinical diagnosis encompassed eye and genetic evaluations described previously (15).

4. Technology

The procedure of pediatric cataract's clinical and genetic diagnosis with WES was the evaluated technology. Diagnosis' protocol was divided into 9 steps: 1. Pre-test clinical evaluation; 2. Peripheral blood samples collection; 3. Genomic DNA extraction and genomic DNA evaluation of quantity and quality; 4. Library preparation; 5. Exome sequencing; 6. Bioinformatics analysis; 7. Sanger sequencing for validation of suspected pathogenic variants 8. Post-test clinical consultation; 9. Operational step for the network organization and biologic material transportation (Fig. 1).

A theoretical network of the main 12 governmental tertiary hospitals with pediatric cataract patients eligible for ocular genetic testing was created in the city of Rio de Janeiro (Fig. 2). Two other facilities (A and B) were selected as hubs. Hospital A to be responsible for steps 3, 6, 7 and 9, and hospital B for steps 4 and 5 (Fig. 2). The remaining 12 facilities (C-I) would care for the pre and post-test clinical evaluation (steps 1 and 8) as well as the collection of peripheral blood samples (step 2) which would then be referred to the hubs.

5. Cost analysis scenarios

We estimated the cost of clinical and genetic diagnosis of hereditary pediatric cataract in two scenarios. The first scenario, our reference scenario, included all patients with pediatric cataract and two more family members (one affected and one unaffected) in the city of Rio de Janeiro. We assumed trio analysis for WES. The second scenario, an alternative scenario, considered 5,280 WES exams per month for any genetic disease working within the hub.

6. Microcosting model

A theoretical study model was created based on population, epidemiological parameters and assumptions. Population parameters considered that 76% of the population use SUS, based on official governmental data from Rio de Janeiro city. Diseases’ epidemiological parameters included pediatric cataract prevalence of 3.46:10,000 and incidence of 1.03:10,000 (16).

The horizon time was of five years as the first year took into consideration the acquisition cost of the equipment plus consumables and staff and the second year included consumables and staff. The model included data of incidence and prevalence.

Every step of the genetic testing protocol was parsed into an Excel spreadsheet to identify, quantify and value each item used in the procedure. Direct costs of each step included costs of disposable consumables, frequency of equipment use and of hands-on staff time. If available, components were priced using an official database. If not, they were priced according to the manufacturer or wholesale suppliers’ information. Overhead costs, including infra-structure water, cleaning, electricity, safety and other items were assumed as 10% of the cost per exam and were included in operational step costs.

Consumable costs were reduced to a per-unit cost (per exam). To estimate each step cost, the necessary item cost per-unit was listed and multiplied by the minimal batch quantity needed for the eligible population.

To reach the equipment estimative cost, we listed all the equipment used and distributed them between the two main facilities (A and B) according to the steps. We assumed that the sequencer Illumina NovaSeq6000 (facility B) would work in high performance with the following characteristics:
2 x 100 base pairs coverage, S4 flowcell two plaques with 240 samples each, for 36–48 hours, 22 days per month. Given this, the maximum monthly capacity of the sequencer in this hub would be 5,280 samples ([240 samples per plate x 2 plates X 22 workdays in a month]/2 days which is the longest duration of the sequencing). This included not only pediatric cataract patients but also patients with other rare and prevalent diseases with indication of genetic testing. For other equipment, we estimated the quantity needed to perform 5,280 samples monthly, assuming maximum performance in a 40-hour-week workload, during 22 days per month. Equipment was annualized at a 5% discount rate as needed. Equipment was priced according to the manufacturer or wholesale suppliers’ information. Annual maintenance was estimated at 5% of the equipment price.

To estimate the cost per step if one equipment from the same facility was used in more than one step, we assumed a pro rata distribution to adjust its cost by the equipment usage percentage.

The annual salary of each personnel job class was obtained from hospital’s A data as this ward would be responsible for the main steps. To obtain the real annual salary, the monthly wage was multiplied by 14.3 in accordance to Brazilian Labor Law. This adjustment included 1/3 of the monthly salary for vacation, a thirteenth salary for December and a one month payment for a staff substitute during mandatory vacation. We assumed a 40-hour per week workload and 54 weeks per year. The personnel would perform the specific step for 6 hours a day with the remaining 2 hours for computer work and lunchtime. We estimated weekly, monthly and annual productivity per personnel according to the hands-on time per step.

Logistic estimative cost included the cost of transporting patient’s blood samples from tertiary hospitals to the hub hospitals. Hospital A would receive samples to perform DNA extraction, library preparation and, after whole exome sequencing, Sanger sequencing. Next, hospital B would receive the products for library construction and whole exome sequencing.

In our reference scenario, considering pediatric cataract patients, we assumed the frequency of transportation based on the activity of each pediatric ophthalmology department. Hospitals with lower activity would need transportation once every 3 months; hospitals with moderate activity would need transportation once a month and the one with high activity, twice a month. The Google Maps platform was used to calculate the distance among the units, assuming a car performance of 8 km per liter for gasoline cost estimator. We also assumed it would be possible to use one of the available cars at hospital A. Staff included one hired driver for these periods.

We considered the exchange rate 1.00 USD = R$5,1686 (from January 2022-June 2023) (17). Model data is available upon request.

7. Outcome

The primary outcome was the cost per clinical and genetic diagnostic exam with WES of pediatric hereditary cataracts. The secondary outcome was the cost per step.

8. Sensitivity analysis

We conducted a one-way sensitivity analysis for fluctuations in unit costs of the most expensive consumables (+ 30% and – 30%), of staff (+ 30% and – 30%) and of equipment (+ 100% and – 20%). These ranges were chosen arbitrarily.

Results

Table 1 shows the following costs per patient for reference and alternative scenarios, considering the five-year horizon: average cost for clinical and genetic diagnosis of hereditary pediatric cataracts, pre-test clinical consultation, peripheral blood samples collection, genomic DNA extraction, library preparation, WES, bioinformatic analysis, Sanger sequencing, operation cost, post-test cost. Considering only WES, the cost per exam was of 455.29 United States Dollars (USD) for the reference scenario and 386.98 USD for the alternative one. For the reference scenario, consumables represented 72% of the genetic testing cost, followed by 14% for staff, 5% for equipment and the other 9% for overhead cost. Taking into account the alternative one, consumables represented 84%, staff 5% and equipment 2% of the cost per exam. Overhead cost represented the other 9%.

Sensitivity analysis showed that the most important costs were consumables in the reference and in the alternative scenarios (Figs. 3 and 4). Assuming a 30% increase in consumables’ cost, the cost per exam increased 20% in the reference scenario and 23% in the alternative. On the other hand, even when doubling the equipment cost, the cost per exam only increased 5% in the reference scenario and 2% in the alternative scenario.
Table 1
Cost of pre test and post test clinical evaluations and cost per step of whole exome sequencing of hereditary pediatric cataract. Cost of whole exome sequencing discriminated by consumables, equipment, and staff in the reference and alternative scenarios.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Test</th>
<th>Peripheral Blood Collection</th>
<th>DNA Extraction</th>
<th>Library Construction</th>
<th>NGS Sequencing</th>
<th>Analysis</th>
<th>Sanger Sequencing</th>
<th>Post Test</th>
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<tr>
<td>Total Cost per Exam</td>
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<td>USD 22.21</td>
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<td>USD 48.25</td>
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<td>USD 2.56</td>
<td>USD 541.20</td>
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*Equipment Cost = Average of 5 years (1st year cost + 4 x 2nd Cost)

**Considers a 10% Overhead cost overall and the average equipment cost

Discussion
To the best of our knowledge, this is the first study that estimates the cost of WES for hereditary pediatric cataract from a middle-income country perspective. Accurately estimating WES cost can be difficult due to the many steps involved, the variations in available resources or on the researcher’s preferences and the organization of the healthcare network. Nevertheless, it is a major step for planning resource allocation in any sustainable healthcare system, particularly in limited-resource settings (9, 18).

Along with the cost per exam of exome sequencing, this study has also proposed a theoretical network care which included the logistics for delivering samples between the facilities of the hub. The network was structured for pediatric cataract patients, but it could be extrapolated to other ocular genetic diseases such as inherited retinal dystrophies or even non-ocular diseases.
One may argue that genetic testing of pediatric cataract patients should not be a priority because its diagnosis is clinical, and its surgical treatment does not depend on the variant identification. Although these two statements are in fact, true, they should be considered in a broader scenario. Genetic testing is important since up to 30% of pediatric cataracts are inherited (2). The identification of the causative variant and its pattern of inheritance are fundamental to improve genetic counseling and community education. In our cohort, 13 out of 29 families had three or more affected members that would benefit enormously from precise genetic counseling and genetic follow-up.

In addition, 15% of pediatric cataracts are a manifestation of systemic diseases, and cataracts may be one of the first clinical findings, such as in galactosemia, Lowe or Alport syndromes (2). Lenassi et. al. showed that genetic testing in bilateral pediatric patients avoided unnecessary tests in 50% of them (10). As an example, one patient from our cohort had unnecessary phlebotomies and used prolonged oral iron chelator for having hyperferritinemia, which was then diagnosed as hereditary hyperferritinemia-cataract syndrome after genetic testing (19).

Moreover, variant identification in affected families reduces anxiety and enables validation of a clinical diagnosis as well as a feeling of belonging for having a final diagnosis, especially for diseases that have no treatment (3), but also for the ones that do, such as pediatric cataracts.

Questions regarding affordability of pediatric cataract genetic diagnosis are raised and there is scarce information about its cost. A recent systematic analysis of microcosting estimation for genome and exome sequencing did not include any publication for pediatric cataract patients (20). In addition, no publication from middle-income countries was included (20), suggesting an uneven distribution of genetic cost information.

In the reference scenario, we have estimated the clinical and genetic diagnosis for pediatric cataracts costs at 609.51 USD per patient under the SUS perspective. This estimation included pre-test and post-test consultations and complementary exams. Considering only genetic testing with whole exome sequencing, the cost would be 455.29 USD per patient.

In the literature, there is considerable variation among microcosting estimates for different diseases (9, 20). Cost estimation for rare diseases ranged from 993.00 USD per patient for germline mutation to 3,388 USD per patient for neurodevelopmental disorders of unknown genetic etiology in high-income countries (20). Each disease has a specific strategy for analysis which impacts the genetic testing cost. Nevertheless, consumables from library preparation and sequencing were responsible, proportionally, for most of the costs, as in our study (21). Even in a worst-case scenario when we doubled the equipment’s acquisition cost in the sensibility analysis, the consumables’ representation of the whole exome sequencing cost decreased to 68%.

Interestingly, the cost of WES is likely to depend on the diagnostic yield (22). Considering the concept of cost per positive diagnosis, the greater the number of conclusive variants found, the lower the cost. This is calculated by dividing the per-patient cost of delivering molecular testing by its diagnostic yield. In our case, the cost per positive diagnosis would be approximately 734 USD considering our diagnostic yield of 62%. When taking into account a high diagnostic yield of 80% for inherited dystrophies (23), the cost would be 659.11 USD. The more expertise gained, the lower the final cost and the greater the test’s clinical utility over time.

Genetic testing with WES for rare diseases and cancer is available in many high and middle-income countries, although availability does not always translate into public utilization (24). National initiatives in the United Kingdom and France aim to strengthen Genomic Medicine in their public healthcare systems (5, 6). Following this trend, the Brazilian government launched the "Genomas Brasil" national program in 2020, with the objective of creating foundations and expertise for precision medicine within SUS through genomic (11). This study is aligned with the project by providing a microcosting evidence of whole exome sequencing’s cost for pediatric cataract.

Brazil has a "National Policy for Comprehensive Care of People Affected by Rare Diseases within SUS" which has been promoting healthcare equity for these patients since 2014. It addresses comprehensive and multidisciplinary care including diagnosis, genetic counseling, treatment and rehabilitation (25). Although 80% of rare diseases are genetic and there are 33 genetic services in SUS, it is estimated that only half of them perform molecular biology techniques for genetic investigation (13, 26).

Pediatric cataract prevalence is estimated to be 3.46:10,000 children and, for that reason, it is a rare disease according to the definition of the Brazilian Ministry of Health (16) (MS SUS). Despite this, patients with hereditary pediatric cataract and other genetic rare eye diseases are cared for in ophthalmological services and their genetic diagnosis is still challenging. It was estimated that rare diseases reference centers serve one third of their (non-ocular) demand (13, 26), becoming a major bottleneck for patients with rare ocular diseases that also have access to them.

Furthermore, there is no expected reimbursement value for performing WES within SUS’s clinical practice (27). Brazilian federal government pays up to, approximately, 620 USD per patient with a rare disease per year, but this should include costs for his/hers diagnosis, treatment and rehabilitation. If WES is necessary and available - it should be included in this budget. Considering our estimation of 455.29 USD per WES for pediatric cataract in the base scenario, the reimbursement for rare disease patients might be underestimated. However, as one of the main principles of SUS is the decentralization of health care assistance, municipalities and states should also contribute to health care financing (28).

The evolving nature of high-throughput NGS with improvements in the sequencing chemistry and technology, as well as bioinformatics and data interpretation, has enabled a higher volume of testing in a shorter time. Also, higher-resolution diagnoses are expected to reduce diagnostic and treatment odysseys (18).
Given that, we also created a theoretical high-performance scenario, functioning within an existing hub that sequences different diseases, rare and prevalent (14). In this alternative scenario, the cost per exam would be 386.98 USD. This means that performing the test on a large scale improves not only its affordability by decreasing its cost per exam by 15%, but also increases the patients’ access to precision medicine.

For example, the sequencer equipment can cost approximately 965,500 USD and has a capacity of up to 5,200 exams per month for any disease. Considering its use for only pediatric cataract and family members in Rio de Janeiro city (250 exams per month) and not for other diseases, the cost per exam of WES would be 555.96 USD with 58.4% from consumables, 20.5% from equipment and 12.1% from staff. From the SUS standpoint, other patients with genetic diseases should also profit from this equipment's capability. As in our base and alternative scenarios, structuring a hub is the solution to enhance access and gain efficiency while reducing the cost per exam. Familial dyslipidemia and genetic cardiomyopathies are some of the many non-rare clinical indications currently sequenced in our current hub (14).

Brazil is a continental-size country with 160,000,000 people depending on SUS. Detailing and obtaining the cost of each step of the exam can help policymakers to structure a roadmap for the rational utilization of WES. Also, using the capillarity of SUS's network – which is as high as 40,000 basic units across Brazil (29) – could be a key element to reach all Brazilians that could benefit from WES. It is crucial to develop a national genomic industrial framework in order to avoid the risk of being in a technological disadvantage compared to other countries (18).

Our study has some limitations that should be pointed out. Firstly, we used microcosting estimation technique, which is often non-generalized as it is specific for each setting, albeit being an accurate and discriminating technique. Secondly, the imported equipment and consumables prices may vary due to exchange rates, especially in low and middle-income countries. Usually, larger orders allow better negotiations with suppliers, decreasing the price of consumables. Thirdly, we performed the estimation in one setting, the Rio de Janeiro municipality, and for one disease: pediatric familiar cataract. However, while the genetic knowledge and diagnostic strategy for each genetic disease is different, the basic technological resources for molecular testing are shared, thus being an opportunity for its cost estimative extrapolations to other diseases.

There are some remaining challenges to incorporate genetic testing for pediatric cataracts in the clinical practice of a middle-income country. The need to keep up with the exponential advances of the technologies and bioinformatic pipelines is one worth mentioning. Also, shortage of experienced professionals such as bioinformaticians can be a major barrier, although it can also be an opportunity to improve training and expertise. Concerns regarding data privacy, evidentiary uncertainty and accidental findings are common challenges expected in any genetic testing and there should be protocols to guide the team on how to proceed. Patients’ pathways and referrals would need to be redesigned to include the test in the clinical routine. The genetic network would have to deliver timely results to guarantee the best clinical outcome and efficiency. Other studies focusing on clinical utility, cost-effectiveness, burden of the disease and budget impact analysis are also needed to support policymakers with the decision-making puzzle in healthcare.

Whole exome sequencing for familial pediatric cataract within SUS could be used as bedrock for other ocular genetic diseases, such as retinal dystrophies, which need molecular diagnosis for currently available gene therapy such as Voretigene or for inclusion in ongoing clinical trials (30). More importantly, it can create an opportunity to accelerate the access of genetic testing in the routine clinical practice to other rare or inherited diseases and cancers.

Inevitably, genetics will be the standard of care and should be available for the community of patients. Accurate information regarding cost estimation of genetic testing can aid healthcare policymakers from middle-income countries in their resource-use assessment for governmental decision-making.

**Declarations**

**Compliance with Ethics Guidelines**

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

**Ethics approval**

The study was approved by the Ethics Committee of INSTITUTO FERNANDES FIGUEIRA-IFF/FIOCRUZ-RJ/MS (protocol code 21444619.0.0000.5269), 17 October 2019.

**Consent to participate**

Informed consent was obtained from all patients for being included in the study.

**Conflict of interest**

The authors declare that they have no conflict of interest.
Luiza M. Neves declares she has no conflict of interest.

Márcia Pinto declares she has no conflict of interest.

Olivia A. Zin declares she has no conflict of interest.

Daniela P. Cunha declares she has no conflict of interest.

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Leonardo H. F. Gomes declares he has no conflict of interest.

Dafne D. G. Horovitz declares she has no conflict of interest.

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References


Figures

Figure 1

Diagnosis protocol of pediatric cataract comprising 9 steps: pre-test evaluation, peripheral blood collection, transportation of biological material, DNA extraction, library preparation, next generation exome sequencing, bioinformatic analysis, Sanger sequencing, post-test clinical evaluation.
Figure 2

Twelve governmental tertiary hospitals with pediatric cataract patients eligible for ocular genetic testing in the city of Rio de Janeiro (figure 2). Hospitals A and B are hubs.
Figure 3

Tornado diagram of parameters (equipment, staff and consumables) impacting on the cost per exam in the reference scenario. X axis represents the impact on cost per exam in U.S. dollars of each parameter variation, and Y axis represents baseline parameters with the cost of whole exome sequencing per exam of 455.29 USD. Orange and blue bands show each parameter high and low values, respectively. The number next to each band corresponds to the cost per exam of whole exome sequencing in U.S. dollars of that parameter after the sensitivity analysis.

Figure 4

Tornado diagram of parameters (equipment, staff and consumables) impacting on the cost per exam in the alternative scenario. X axis represents the impact on the cost per exam in U.S. dollars of each parameter variation, and Y axis represents baseline parameters with the cost of whole exome sequencing per exam of 386.98 USD. Orange and blue bands show each parameter high and low values, respectively. The number next to each band corresponds to the cost per exam of whole exome sequencing in U.S. dollars of that parameter after the sensitivity analysis.