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Research Article

Costs of genetic testing: Supporting Brazilian Public Policies for the incorporating of molecular diagnostic technologies

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Abstract

This study identifies and describes the operating costs associated with the molecular diagnosis of diseases, such as hereditary cancer. To approximate the costs associated with these tests, data informed by Standard Operating Procedures for various techniques was collected from hospital software and a survey of market prices. Costs were established for four scenarios of capacity utilization to represent the possibility of suboptimal use in research laboratories. Cost description was based on a single site. The results show that only one technique was not impacted by rising costs due to underutilized capacity. Several common techniques were considerably more expensive at 30% capacity, including polymerase chain reaction (180%), microsatellite instability analysis (181%), gene rearrangement analysis by multiplex ligation probe amplification (412%), non-labeled sequencing (173%), and quantitation of nucleic acids (169%). These findings should be relevant for the definition of public policies and suggest that investment of public funds in the establishment of centralized diagnostic research centers would reduce costs to the Public Health System.

Keywords: molecular diagnosis, hereditary cancer, cost analysis.

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Introduction

Over the past several decades there has been a significant increase in the number of medical consultations and hospital admissions due to genetic diseases, especially in large centers and reference hospitals in Brazil (Horovitz *et al.*, 2013). Diagnosis and genetic counseling for individuals and families with genetic diseases involves, in most cases, laboratory exams in the areas of biochemistry, cytogenetics and molecular genetics. Public and private medical services specialized in medical genetics are mainly located in large urban centers, primarily in public and academic institutions that are not always equipped with laboratories and staff to provide the genetic testing needed for diagnosis (Melo and Sequeiros, 2012; Toledo *et al.*, 2012). Furthermore, molecular diagnostic technologies were not added to the list of procedures of the Brazilian Public Health System (SUS) until 2014, and only rare diseases were included at this time. In addition, molecular screening for hereditary cancer was not included as a compulsory coverage procedure of the Brazilian National Health Agency (ANS) until 2012. Therefore, access to these exams is still very limited for the population as a whole (Horovitz *et al.*, 2013; Vieira *et al.*, 2013).

Estimating the costs of these new technologies would aid in the development of better strategies to enable wider access and equity of care. With the aim of providing support to the development of public policies aimed at the inclusion of new molecular diagnostic technologies in the SUS, a multidisciplinary working group evaluated operating costs for different methodologies, using diagnosis of familial cancer as a case study.

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Although most cancers result from complex interactions between the genetic composition of the individual and the environment, a small percentage of cancers are primarily due to inherited changes that confer a high predisposition to the disease. Individuals with hereditary forms of cancer develop one or more tumors at a young age, and can transmit this predisposition to their descendants. Today it is estimated that at least 5-10% of all tumors are associated with inherited genetic disorders, and over 50 distinct syndromes have been described as conferring a predisposition to cancer (Lindor *et al.*, 2008; Weitzel *et al.*, 2011). From the identification of a gene to cancer predisposition, a number of procedures are available that contribute to the best patient care. Among them, molecular diagnostics and predictive tests are available, which are important for clinical assessment and genetic counseling programs for families at risk. These tests are also considered in the preparation of guidelines for screening, early diagnosis and prevention of cancer in these cases (Garber and Offit, 2005; Meiser *et al.*, 2006; Schmidtke and Cassiman, 2010). For example, identifying a germline mutation in the *BRCA1* gene, which predisposes the patient to breast cancer, guides the referral to a specialized screening program. This includes an earlier start of mammography, additional imaging tests such as MRI of the breasts with contrast, and discussion of prophylactic mastectomy and salpingo-oophorectomy in women aged 35-40 years. On the other hand, testing negative for a mutation in *BRCA1* allows the patient to be monitored in the same manner as any other woman of the same age in the general population, freeing her from intensive screening and decreasing the burden to the health system.

Nonetheless, at present there is no health policy for inclusion of individuals with hereditary risk for cancer in the Brazilian Public Health System (SUS), which evaluates the cost-effectiveness of preventive methods and early diagnosis in these individuals by comparison to the treatment and rehabilitation of cancer patients. Estimating the operating costs of genetic tests needed for familial cancer diagnosis is an essential step in this process. In this article, we describe the estimated operating costs for molecular diagnostic testing of several diseases prioritized by the National Familial Cancer Network (INCA, Ministério da Saúde, 2009)

Methods

This is a descriptive and quantitative study performed in 2012 under the auspices of the Public Health System (SUS) as a public service provider. The study utilized data from Hospital de Clinicas de Porto Alegre (HCPA), a public university general and high complexity hospital with patient care, teaching and research activities. The main figures used in this study were based on a literature review of cost calculation, ownership legislation prevailing in the country, and management in health care services (Brazil, 1990, 2004; Martins, 2001; Muenning, 2008; Brazilian Health Ministry, 2009; Balbinotto and Jardim, 2013).

Data collection

Most management parameters at HCPA are accessible by computer, and the databases of two consolidated management tool software programs used at the hospital were used as the data source. To obtain direct costs of diagnostic procedures, the database of the 'Application for Hospital Management' (AGH) software program was used. Indirect costs were obtained through, the 'Management Information System' (IG) program, which contains a specific cost module called 'Absorption Cost System'. It corresponds to the Business Intelligence System widely used in business management (Elbashir *et al.*, 2011; Duan and Xu, 2012). Both software programs housed data for the period of January to December 2012.

The Standard Operating Procedure (SOP) of each technique was used to estimate costs of different techniques, using the latest version available in the laboratory. The tests were monitored by the researcher to confirm the validity of the SOP. This was also used as a guide for setting the maximum capacity, which consisted of determining the maximum number of samples that could be processed for a technique given full capacity operation of equipment and an eight-hour work day. This number was designated as 100% usage of available capacity. For example, for DNA extraction using a GE kit, 12 blood samples was considered 100% capacity, because this is the maximum number of samples that could be processed simultaneously in the available microcentrifuge. Thus, for each technique, the value of 100% capacity is dependent on the equipment used. For comparison purposes, the analysis of 70%, 50% and 30% of available capacity scenarios was defined *a priori*. To calculate cost in these scenarios, variable costs were adjusted accordingly (for instance, half of the kit is used for six blood samples), whereas invariable costs were held constant (the amount of work hours is the same whether 12, six or three samples are processed). The performance of multiple techniques on a single machine [*e.g.*, a Genetic Analyzer used to perform assays of microsatellite instability (MSI), multiplex ligation probe amplification (MLPA) and DNA sequencing] required the distribution of total usage hours per month at 100% capacity among the techniques; equal division among techniques was used in this model.

Cost analysis

Direct costs included raw materials and supplies, hired personnel, equipment depreciation, general expenses, telephone, electricity and water (the last two cost items were prorated according to the area in square meters of the laboratory where tests are performed). In the estimates presented here, the direct costs of raw materials and supplies were also based on the SOP for the technique.

For each technique, consumables and quantity required for implementation were listed, and the price of materials was set at the market value of the last purchase made by the hospital. For products obtained on the Brazilian market, information was obtained from AGH software. For imported products, an updated invoice for direct import was requested and the value converted into Brazilian currency at the commercial exchange rate on the date of the proposal, and 30% was added to cover additional costs of import. It is worthy of note that imports made for research purposes benefit from tax exemptions according to current law (Brazil, 1990, 2004).

Direct costs were prorated by the number of samples processed in the laboratory according to the full capacity of the equipment. To determine the cost of personnel, the basic gross salary of professionals involved in performing the test was used and social security charges and hourly wage was calculated. The costs associated with analysis and interpretation of genetic testing or with administrative staff and other areas of organizational structure were not considered. The cost of equipment depreciation was obtained from the information generated by the patrimonial control department of the hospital; the acquisition cost of the equipment was not included. Additionally, a value of 10% (overhead) on the total amount of direct costs was defined *a priori*, referring to the losses of consumables that occur during the execution of techniques.

Indirect costs included cleaning, building maintenance, property security, and energy were and obtained from the IG software. As these costs are determined by the size of the laboratory space, the total cost incurred by the institution housing the laboratory was divided by the size in square meters of the laboratory itself, such that only the cost for the laboratory used was considered. In the case of a multi-user laboratory, many projects utilize the equipment available, which led to the definition of an indirect cost per project (total overhead cost per square meters of laboratory and per monthly average of projects), an amount allocated to all techniques due to lack of information that would allow prorating for technique. Furthermore, we included the costs of occupational medicine, which in software IG are allocated according to use by employees.

Techniques, tests and exams in oncogenetics

As stated above, the first step in cost analysis was estimating costs per laboratory technique and subsequently calculating costs for tests and exams. The costs per test include the combined use of several techniques on the same sample to obtain a result [for example, DNA sequencing requires prior performance of a polymerase chain reaction (PCR), and the latter requires the prior performance of DNA extraction]. The exam is the ensemble of tests required for the evaluation of a diagnostic hypothesis in one patient. It includes, besides the collection of biological samples, confirmatory analyses whenever necessary. The ten diagnostic tests included in cost calculation of the present study were those identified as priorities by the National Familial Cancer Network. The overall design summarized in Table 1 includes the different stages considered in the calculation of operating costs..The description of the components that were considered in the cost analysis is depicted in the Supplementary Material (Tables S1-10).

Results

The initial stage of pricing techniques was performed based on the assessment of SOP, including not only the cost of reagents but also that of personnel and indirect costs as mentioned above. Cost description was based on a single site. Eleven different techniques prioritized by the National Familial Cancer Network were selected. As an example, Table 1 presents the estimated cost of one these techniques, the polymerase chain reaction (PCR). The average cost to the public health system for PCR assay of one sample is US$ 1.58.

At first, costs were established by assuming 100% capacity, a strategy that maximizes resource use but does not always represent reality in research or diagnostic laboratories. Thus, costs were also calculated for three other scenarios at lower capacity. As shown in Table 2, the cost of only one technique - immunohistochemistry analysis using a panel of four antibodies for the identification of DNA mismatch repair (MMR) deficiency- was unaffected by sub-

Table 1 - Cost calculation for polymerase chain reaction (PCR) technique.

Polymerase chain reaction (PCR): 40 samples			
Material	Measure	Amount	Cost US$
Biologist	hour	1	13.00
Gloves	pair	1	0.21
Yellow tips 0-200 μL	unit	7	0.12
Colorless tips 0.5-10 μL without barrier	unit	40	0.67
Microtube 1.5 mL	unit	1	0.02
Microtubes 0.2 mL	unit	40	1.52
dNTPs 10 mM	μL	20	3.09
Forward oligonucleotide 20 pmol	μL	20	3.07
Reverse oligonucleotide 20 pmol	μL	20	3.07
Platinum *Taq* DNA polymerase	μL	2	2.65
Sterile distilled water for c/1000 mL	μL	760	0.00
Electrophoresis for 40 samples	samples	40	21.34
Gel staining for 40 samples	samples	40	4.92
Losses (10%)			5.37
Indirect Costs			4.18
Total for 40 samples			63.23

(*)Total cost of PCR for 40 samples, which in this case is considered equivalent to 100% use of the installed capacity; cost per sample is US$ 1.58.

optimal capacity. Most techniques showed greater variation in cost at 30% of available capacity, including MLPA (412%), conventional PCR (180%), microsatellite instability (181%), sequencing of unlabeled samples (173%), and quantification of nucleic acid (169%). For MLPA, because the number of control samples required does not change in proportion to the number diagnostic samples, performing this test at 30% capacity is unfeasible from an economic point of view (Supplementary Table S11).

The cost of a test was calculated from the sum of the techniques needed to obtain a result that is provided to the patient. Table 3 shows the estimated cost for *BRCA1* gene testing. The cost of each procedure involved depends on the combination of tests requested on the basis of clinical suspicion and indications of the genes to be analyzed in each case and is estimated to be US$ 1,856.61 per exam. An important point to highlight is that the overall cost submitted for complete analysis of the *BRCA1* and *BRCA2* genes is the cost of analysis for the index case in a family. Once a mutation associated with familial risk has been identified, other family members need only be tested for that particular mutation, making costs associated with screening significantly lower (Table 3). This is the strategy recommended by good practices and used in all molecular tests reported here.

Discussion

Although it has traditionally been considered a procedure of high complexity and cost, molecular genetic testing is a key step in the diagnosis of most genetic diseases. Genetic testing is also crucial for predictive diagnosis of some diseases and for evaluating family members at risk. In the latter it is possible to define the presence of genetic risk prior to clinical onset of the disease and to consequently intervene to reduce risk. Cost analysis of genetic testing can provide a benchmark for developing remuneration policies for laboratory activities because there is great heterogeneity of existing public and private diagnostic services, both in adequacy of laboratory methodologies and in the price of services provided. Cost analysis will also be an essential step to support other studies of cost-effectiveness and cost-benefit relations in the future.

In the approach presented here, an estimated cost of genetic testing that reflects key components of the analysis based on direct (*e.g.*, blood sampling, purchase of raw materials and supplies, hired personnel, equipment depreciation, losses of 10%) and indirect (*e.g.*, structure and building maintenance) costs was performed. We did not find studies in the literature with the same degree of detailing costs that we provide in this study. We did find some studies that used similar criteria in the collection of data, such as the cost of materials, staffing, and the use of market prices for calculation of the costs (Lawrence *et al.*, 2001; Holland *et al.*, 2009; Najafzadeh *et al.*, 2012; Wang *et al.*, 2012). It is important to emphasize that this study is limited by its approach, which could be considered only the first in a series of economic analyses, and by the fact that only one type of laboratory structure at one institution was used in these estimations. Although these costs will not directly apply to all other institutions, we are confident that our data and approaches may yield valuable information that can be used in and by other institutions, and can be applied to related scenarios involving clinical genetics testing.

Two factors can be considered the main determinants of the cost values obtained in this study: the use of the available capacity and the sequencing methodology used. The volume of analysis has a large impact on cost, mainly due to the value of manpower for execution of the different techniques. Unlike the time needed for analysis and interpreta-

Table 2 - Change in costs (%) according to the use of available capacity.

Technique	Available capacity		
	70%	50%	30%
Conventional PCR (per amplicon)	32.2	94.4	178.3
Whole blood DNA extraction (column kit)[1]	21.5	44.1	88.1
Whole blood DNA extraction (salting out)[2]	10.2	21.9	47.6
FFPE tissue DNA extraction (specific kit)[3]	12.4	24.8	49.6
Quantification of nucleic acids[4]	31.0	70.9	168.8
Gene rearrangement analysis by MLPA[5]	27.6	74.9	412.3
Amplicon purification for sequencing[6]	15.1	33.1	80.2
Sanger sequencing (per amplicon)	31.4	128.6	172.8
Microsatellite instability analysis[7]	28.0	69.7	181.1
Imunohistochemistry (panel of 4 antibodies)	0	0	0

Legend. PCR: polymerase chain reaction; DNA: Deoxyribonucleic acid; MLPA: Multiplex ligation probe amplification; (1) commercial kit GE; (2) commercial kit Puregene, Gentra; (3) commercial kit QIAgen; (4) using NanoDrop equipment; (5) MRC-Holland commercial kit; (6) using exo-sap method; (7) commercial kit Promega.

Table 3 - Cost calculation for the complete analysis of the coding sequence of *BRCA* genes by Sanger sequencing using 100% of installed capacity.

Hereditary breast and ovary syndromes mutation analysis in *BRCA1* and *BRCA2*		
Technique	Amount	Total US$
Blood draw	1	2.21
Whole blood DNA extraction	1	11.85
Conventional PCR per amplicon	80	233.88
Amplicon purification for sequencing	80	49.65
Bidirectional sequencing and interpretation	160	1558.13
Report printing	1	0.90
Total		1856.61
One mutation		28.18

tion of the results, the time spent preparing 12 or six samples is almost the same. Moreover, some techniques increase costs due to the need for reagents with a fixed volume that do not change when reducing the number of tests (*e.g.*, sequencing) and the apportionment of overhead costs, which also remains unchanged. These findings can contribute to the definition of public policies, and suggest that investment in this area should be allocated to the creation and consolidation of research centers for diagnosis that can receive samples from different localities in a region or state, or even from different regions in the country, thereby reducing costs to national health systems, in this case the Brazilian SUS. In addition to reducing costs, this strategy also benefits from increased expertise in interpreting results, which is a highly complex process. A similar strategy has been successfully implemented in different countries (Bourret *et al.*, 2006; Ontario Cancer Genetics Network, 2013).

The second cost determinant is the central gene analysis methodology used in this study: Sanger sequencing. Despite its considerable cost, this approach is used because it is still considered the gold standard technique in molecular diagnostics, including cancer genetics, and its clinical utility has been clearly demonstrated with high sensitivity and specificity and largely validated by international quality control programs. However, emerging technologies such as next-generation sequencing are now close to matching Sanger sequencing in sensitivity and specificity and can provide the same result at a significantly lower cost, with the additional advantage of the possibility of simultaneous analysis of multiple regions of the genome. The validation of these new technologies and their implementation into clinical practice are in progress at this time in various countries, and their definitive inclusion into clinical practice is likely to occur within the next few years (Bourret *et al.*, 2006; Wang *et al.*, 2012).

Conclusion

This study identifies and describes the operating costs associated with the molecular diagnosis of genetic diseases. Two main factors were identified as main determinants of the cost values obtained in this study: the use of the available capacity and the techniques used for genetic testing. Although the molecular biology techniques evaluated in this study are presented in the context of hereditary cancer diagnosis, they can be applied to the diagnosis of many other inherited diseases. Thus, the scope of the results presented here extends beyond tests involving cancer genetics, and the data can be extrapolated to other clinical situations in which molecular analysis of germline mutations is crucial for differential or predictive diagnosis and for choosing a therapeutic strategy. Calculating the costs associated with diagnostic tests by considering their standard operating procedures can help to standardize these surveys in future studies that analyze the budgetary impact of the inclusion of new molecular diagnostic tests in the Brazilian Public Health System.

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Supplementary Material

The following online material is available for this article:

Table S1 - DNA isolation from peripheral blood (Commercial column extraction kit - GE) for 12 samples.

Table S2 - DNA isolation from peripheral blood (Commercial kit - GENTRA Puregene) for 16 samples.

Table S3 - DNA isolation from formalin fixed paraffin embedded tissue (Commercial kit PROMEGA) for 24 samples.

Table S4 - DNA quantification using the Nanodrop equipment for 100 samples.

Table S5 - MLPA (12 samples and 4 controls).

Table S6 - PCR product purification for 96 samples.

Table S7 - Sanger sequencing 96 samples - unlabelled.

Table S8 - Microsatellite instability (MSI) - (94 samples + 2 controls).

Table S9 - Immunohistochemistry panel - 4 antibodies against MMR proteins, per patient.

Table S10 - Preparation of formalin fixed paraffin embedded (FFPE) tissue for scraping before DNA extraction.

Table S11 - Summary available capacity.

This material is available as part of the online article from http://www.scielo.br/gmb.

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