Viewpoint

National Network of Cardiovascular Genomics: Implementing Genetic Diagnosis in Cardiology in the Brazilian Unified Health System

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The Brazilian National Network of Cardiovascular Genomics (RENOMICA) is a research project whose objective is to establish a proof of concept that genetic diagnosis for hereditary cardiovascular diseases is important, feasible, and cost-effective within the Brazilian Unified Health System (SUS). Funded by the Brazilian National Genomics and Precision Health Program (Genomas Brasil) of the Ministry of Health, the study is coordinated by the Brazilian National Institute of Cardiology (INC), with 21 co-participating centers throughout the country. Recruitment, which began in September 2021, is still ongoing. Research participants, with the assistance of genetic counseling, provide a cheek swab sample that can be collected at home, and the study team performs whole exome sequencing in search of gene variants related to the phenotype. The sequencing results are forwarded to the participants, and, if positive for the investigated disease, family members are invited to participate in genetic screening. As a result, we expect to understand mechanisms of incomplete penetrance and variable expressivity in hereditary cardiovascular diseases, construct an economic model to determine the cost-effectiveness of genetic diagnosis of hypertrophic cardiomyopathy in the context of the SUS, and provide information to the database of the Genomas Brasil Program.

Genetic diagnosis is important

Hereditary cardiovascular diseases (Table 1) are the most frequent cause of sudden death in individuals under 35 years of age, and they remain an important cause of death up to 50 years of age.[1] Although diagnosis of the proband, or index case, can be made clinically, it is only possible to screen family members who carry the gene variant that causes the disease by means of genetic diagnosis. This screening aims to institute measures that prevent sudden death and clinical surveillance in these family members, as well as reproductive counseling, when necessary. Several international guidelines recommend performing genetic diagnosis in different types of hereditary cardiovascular diseases.[2-6] In fact, hypertrophic cardiomyopathy guidelines[2] consider genetic diagnosis a class I, level B-NR recommendation. Furthermore, genetic tests allow differential diagnosis with phenocopies of hypertrophic cardiomyopathy, such as Fabry disease, amyloidosis, PRKAG2 cardiomyopathy, among others. In pediatric patients, genetic testing may be even more important, as it allows the differential diagnosis with inborn errors of metabolism, for some of which there are therapeutic alternatives.

Table 1 – List of hereditary cardiovascular diseases

Group	Disease
Aortopathies	Hereditary thoracic aortic aneurysms and dissections
	Ehlers-Danlos syndrome (vascular form)
	Marfan syndrome
	Loeys-Dietz syndrome
Channelopathies	Progressive cardiac conduction disease
	Long QT syndrome
	Short QT syndrome
	Brugada syndrome
	Catecholaminergic polymorphic ventricular tachycardia
Cardiomyopathies	Arrhythmogenic*
	Dilated
	Hypertrophic
	Non-compaction
	Restrictive
Congenital heart diseases	Miscellaneous† (for example, Holt-Oram syndrome, Noonan syndrome)
Dyslipidemias	Familial hypercholesterolemia
Pulmonary diseases	Pulmonary arterial hypertension

**Previously known as arrhythmogenic right ventricular dysplasia.*
†For review, see reference.[8]

Keywords

Genomics; Heart Diseases; Sudden Death; Exome Sequencing; Familial Hypertrophic Cardiomyopathy.

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Manuscript received February 23, 2023, revised manuscript March 17, 2023, accepted March 17, 2023

DOI: https://doi.org/10.36660/abchf.20230011

In spite of this, genetic diagnosis of hereditary cardiovascular diseases is not available through the SUS or the complementary health system. The private network provides the test at elevated costs, which, associated with the lack of information and training in cardiogenomics, results in the underuse of this test. Although genetic tests are not part of cardiologists' routines, the current recommendation is to carry out periodic clinical screening of all asymptomatic family members of patients diagnosed with hereditary cardiovascular diseases, including children and adolescents.[1-7] Hypertrophic cardiomyopathy guidelines recommend that, at a minimum, electrocardiogram and echocardiogram should be performed every 3 years in pediatric patients and every 5 years in adults, for life.[2] Nevertheless, periodic clinical screening of family members is also uncommon in the Brazilian context.

Genetic diagnosis is feasible

RENOMICA was created to fill this gap. We implemented a national study, with 21 co-participating centers (Table 2) and simple logistics, using the high-capacity next-generation sequencing platform installed at the INC. Samples can be collected at home, by means of a cheek swab, and sent via the Brazilian Post Office. Whole exome sequencing is performed, which analyzes the exons of all protein-coding genes present in human DNA. All research participants undergo pre- and post-test genetic counseling, either in person or online, with the creation of a pedigree, and they receive a report with the test results. The study has already sequenced samples from more than 400 patients, and new participating centers are expected to be included soon.

One of the limitations of the study is the time to return the results, given that the analysis of genomic data is complex, and the classification of gene variants involves manual curation processes, with a review of the literature. In our assessment, the preparation of reports is slower than desirable. We began the study proposing the use of open-source tools for data analysis. However, this approach requires a bioinformatics team with experience in human genomics; availability of these professionals in the market is limited, and it is even more difficult to hire them, due to the lagging values of the grants offered by funding agencies. To reduce the wait time for participants to receive their results, we are beginning to use "software as a service" tools, with artificial intelligence and automated reports. While the sorting of variants remains an essentially manual process, all the other steps in the process have been optimized.

Genetic diagnosis is cost-effective

In addition to being important and feasible, it is relevant for the genetic diagnosis of the proband and their family members to be cost-effective as a public health policy, in order to be incorporated into the SUS. In order to investigate the costs and benefits of this technology in the Brazilian context, RENOMICA has been working on the elaboration of an economic model together with the Health Technology Assessment Center (NATS) of the INC. Preliminary data from this model, based on a micro-costing analysis, estimate that the average cost of complete exome sequencing is 1,779.19 Brazilian reals, which is well below the cost charged by the private network. This cost is also slightly below that reported in the literature.[9] However, the data are prior to the launch of the sequencer installed at the INC, which allowed a significant reduction in costs. Analyzing the impact of genetic testing associated with family screening in the context of hypertrophic cardiomyopathy, we observed potential savings of 878.12 Brazilian reals per individual when compared to clinical screening. Despite the high cost of the genetic test in relation to the fees for consultation with a specialist, electrocardiogram, and echocardiogram performed in the SUS, genetic diagnosis makes it possible to spare family members who do not have the variant that causes the disease from periodic assessment (Figure 1). Not only does this economize resources by ruling out repeat exams throughout the family member's lifetime; it also has an impact on important logistical constraints. In the state of Rio de Janeiro alone, the waiting list, in December 2022, for consultation with a cardiologist and transthoracic echocardiogram had 2,378 and 6,488 individuals, respectively. Genetic* testing makes it possible to select individuals who would benefit from clinical screening, reducing the demand for consultations and procedures and, consequently, reducing health inequity.

Table 2 – List of centers that participate in RENOMICA

Centers with open recruitment	UF
Universidade Federal do Amazonas	AM
Hospital Universitário Professor Edgard Santos	BA
Hospital de Messejana Doutor Carlos Alberto Studart Gomes	CE
Hospital Universitário Walter Cantídio	CE
Instituto de Cardiologia do Distrito Federal	DF
Hospital Estadual Infantil e Maternidade Alzir Bernardino Alves	ES
Universidade Federal do Maranhão	MA
Hospital Felício Rocho	MG
Hospital Governador Israel Pinheiro	MG
Universidade Vale do Rio Doce	MG
Pronto Socorro Cardiológico de Pernambuco Professor Luiz Tavares	PE
Pontifícia Universidade Católica do Paraná	PR
Hospital Universitário Antonio Pedro	RJ
Hospital Universitário Pedro Ernesto	RJ
Instituto Nacional de Cardiologia	RJ
Universidade Federal do Rio de Janeiro	RJ
Hospital Universitário Onofre Lopes	RN
Hospital de Clínicas de Porto Alegre	RS
Instituto de Cardiologia de Santa Catarina	SC
Universidade de São Paulo	SP
Universidade Federal de São Paulo	SP

** Total number of requests on the waitlist per procedure, SISREG Transparency Portal. Accessed on February 23, 2023. Available at https://web2.smsrio.org/*

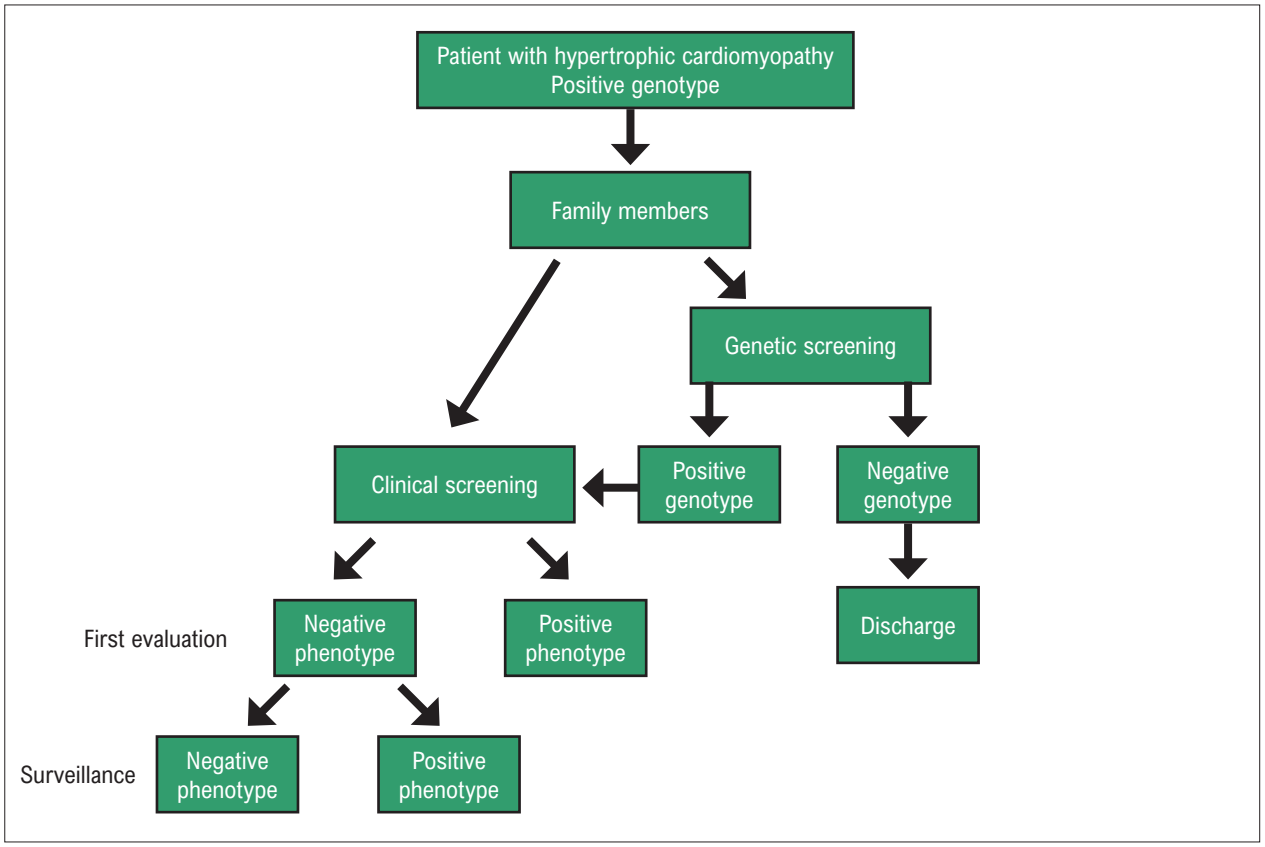

Figure 1 – *Familial screening options in hypertrophic cardiomyopathy. Starting with a proband with a positive genotype, it is possible to opt for clinical or genetic familial screening. In the case of clinical screening, during the first evaluation, some patients may already show signs of ventricular hypertrophy (positive phenotype), while others will have normal ventricular thickness (negative phenotype). In genetic screening, the test determines which family members carry a genotype identical to that of the proband. The chance of a family member carrying the genotype is 50%, seeing that hypertrophic cardiomyopathy is a disease with dominant autosomal inheritance. Family members with a negative genotype can be discharged without undergoing tests. Positive family members begin the clinical screening process.*

Future prospects

Within the setting of RENOMICA, we are working to include an arm for the genetic investigation of sudden death in patients who recovered from sudden death or family members of individuals who died of sudden death before the age of 45. We are also requesting the refinancing of the project for another 2 years from the Brazilian Ministry of Health. Soon, we hope to resume the inclusion of new co-participating centers in the Network.

In relation to the cost-effectiveness study, after completion of the model, we plan to submit a request to the Brazilian Commission for the Incorporation of New Technologies in Health (CONITEC) to incorporate genetic testing for hypertrophic cardiomyopathy into the list of procedures reimbursed by the SUS. Furthermore, we will adapt the economic model of hypertrophic cardiomyopathy to other inherited cardiovascular diseases.

Finally, the expansion of genomic knowledge has created a scenario of subspecialization in Cardiology worldwide, requiring professionals capable of integrating clinical information, obtained from history, physical examination, family history, imaging exams, and functional tests, with genetic information in the diagnosis, prognostic assessment, and family screening of individuals with hereditary cardiovascular diseases.[10] In order to do this, it will be fundamental to establish training programs in cardiovascular genomics so that health professionals can act in the interpretation of tests and genetic counseling, particularly in variants of uncertain meaning, in a multidisciplinary context. The INC will certainly be able to lead this initiative together with other interested institutions.

Author Contributions

Conception and design of the research: and Analysis and interpretation of the data Kasai-Brunswick TH, Campos DBP, Braga AA, Santos MS, Rey HCV, Carvalho AB; Acquisition of data: Kasai-Brunswick TH, Campos DBP, Braga AA, Silva RTB, Sternick E, Carvalho AB; Obtaining financing: Kasai-Brunswick TH, Rey HCV, Carvalho AB; Writing of the manuscript: Kasai-Brunswick TH, Campos DBP, Carvalho AB; Critical revision of the manuscript for important intellectual content: Kasai-Brunswick TH, Campos DBP, Braga AA, Silva RTB, Sternick E, Santos MS, Rey HCV, Carvalho AB.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

This study was funded by Programa Nacional de Genômica e Saúde de Precisão (Genomas Brasil) do Departamento de Ciência e Tecnologia da Secretaria da Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde do Ministério da Saúde.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 42370821.9.1001.5272. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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