

Precision Medicine in Cardiomyopathies

Fernando Rabioglio Giugni¹  and José Eduardo Krieger¹ 

Centro de Medicina de Precisão em Cardiologia (CARDIOGEN), Instituto do Coração (InCor), HC-FMUSP,¹ São Paulo, SP – Brazil

Central Illustration: Precision Medicine in Cardiomyopathies



ABC Heart Failure & Cardiomyopathy

TOOLS

Genotyping

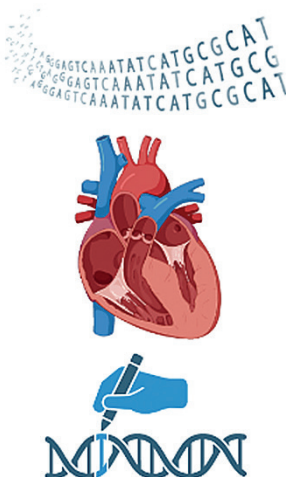
- Next-generation sequencing

Phenotyping

- Biomarkers
- Imaging
- Wearable
- Omics

Advanced therapies

- Gene editing
- Pluripotent cells
- RNA interference



GOALS

- Etiological diagnosis
- Prognostic stratification
- Family screening
- Therapy optimization

ABC Heart Fail Cardiomyop. 2023; 3(1):e20230026

Abstract

Precision Medicine is an innovative clinical approach that uses a wide range of data to assess patients, including genetic and molecular information. Thanks to technological advances and cost reductions, new technologies have been incorporated into clinical practice, such as next-generation sequencing methods. Recently, clinical guidelines have recommended the use of genetic tests in patients with cardiomyopathies, which can have a major impact on etiological diagnosis, prognosis, treatment, and family screening. Furthermore, biomarkers obtained by means of imaging tests, wearables, and omics are becoming increasingly relevant in clinical practice, bringing significant benefits to patients with cardiomyopathies. Promising prospects for new treatments using RNA interference, pluripotent cells, and gene editing should be part of the therapeutic arsenal in the coming

decades. However, there are still challenges to be overcome, such as the need for professional training, the implementation of adequate flows in the health system, and the cost of technologies. Based on this context, this review aims to address different aspects of Precision Medicine and its relevance to the field of cardiomyopathies.

Introduction

Precision Medicine represents an innovative clinical approach that aims to acquire and incorporate a vast amount of patient information, including genetic, molecular, physiological, environmental, and imaging data, to allow for more individualized and accurate diagnosis and treatment.¹ Thanks to the development of sequencing techniques, omics sciences, and computational tools for storing and analyzing data, it has become possible to obtain this information on a large scale. Cardiology is one of the areas that has benefited from this revolution, with the increasing incorporation of new tools in both research and care.^{2,3} In particular, the area of cardiomyopathies is one that has benefited most, with significant advances in etiologic diagnosis, family screening, risk stratification, and targeted therapies. Many of these approaches have already been incorporated into care guidelines, while others are still in the process of being translated.

Keywords

Precision Medicine; Cardiomyopathies; Genetic Testing

Mailing Address: José Eduardo Krieger •

Av. Dr. Eneas C. Aguiar, 44, 10º andar. Postal Code 05403-000, São Paulo, SP – Brazil

E-mail: j.krieger@hc.fm.usp.br

Manuscript received April 14, 2023, revised manuscript April 17, 2023, accepted April 17, 2023

DOI: <https://doi.org/10.36660/abchf.20230026>

Genetic testing

Genetic tests are increasingly relevant in the assessment of patients with cardiomyopathies, and cost reduction and increased availability of next-generation sequencing methods have made it possible to expand their indications. It is essential that the tests performed include evaluation of all genes associated with the identified phenotype in customized panels or in more comprehensive tests, such as whole exome sequencing or whole genome sequencing.⁴

A 2022 consensus produced by arrhythmology societies in Europe, Asia, and Latin America recommends (class I) genetic testing in probands with hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic cardiomyopathy, as well as cascade screening of family members.⁴ The same document suggests (class II) testing for probands with restrictive cardiomyopathy and non-compaction cardiomyopathy and screening of family members. Previous guidelines and consensus from the United States also recommend genetic testing for probands with cardiomyopathies and their relatives.⁵⁻⁷

Genetic testing is essential to identify phenocopies of hypertrophic cardiomyopathy, which are diseases with a similar phenotype, but with distinct pathophysiology and, eventually, specific treatments. Examples of phenocopies of hypertrophic cardiomyopathy include Fabry disease, PRKAG2 syndrome, and Pompe disease, in which there are deposits of other substances inside cardiomyocytes. Another group of diseases that can also manifest as phenocopies of hypertrophic cardiomyopathy is RASopathies, pathologies resulting from alterations in the RAS/MAPK cellular signaling pathway, which manifest syndromic extracardiac alterations in association with myocardial hypertrophy. On the other hand, identification by genetic testing of variants associated with hypertrophic cardiomyopathy confirms the clinical diagnosis and allows better risk assessment with more appropriate use of new therapies such as mavacamten.⁸

In dilated cardiomyopathy, genetic testing has prognostic importance. The identification of pathogenic variants in genes that are more associated with arrhythmias and sudden death, such as FLNC, LMNA, and PLN, confers greater risk to these patients.⁹⁻¹³ The most current recommendations indicate earlier implantable cardioverter-defibrillator implantation in these patients.^{4,14} The interface between dilated cardiomyopathy and arrhythmogenic cardiomyopathy is important, especially in the biventricular or left ventricular form, and genetic testing helps fulfill the diagnostic criteria.¹⁵

Genetic testing is also relevant for identifying patients with transthyretin amyloidosis (ATTR) in restrictive cardiomyopathy, a disease with several effective treatment options, especially in earlier stages of its natural history.¹⁶ In non-compaction cardiomyopathy, the benefits are less established, and there is an important intersection with other cardiomyopathies.⁴

In addition to the benefits of genetic testing for probands, there are also impacts for family members, who may be genetically screened and receive diagnoses in subclinical stages of the disease. Guidelines are unanimous in recommending cascade screening for family members of probands with a positive genetic test, starting with the first-degree and progressing to the second and third, depending on the

results.^{4,7} Anticipative strategies, in which individuals at risk are identified even before the actual manifestation of the disease, are fundamental in health systems, as they allow prioritization and rationalization of resources.

The identification of new genes associated with phenotypes makes it possible to improve the diagnostic accuracy of tests and explore new molecular mechanisms associated with the pathophysiology of diseases, with new potential therapeutic targets. Improving the accuracy of genetic tests involves improving the classification of the variants found, thus allowing an ever smaller number to be classified as variants of uncertain significance.¹⁷ This effort depends greatly on the establishment of large databases including healthy and affected individuals, in diverse populations, with strategies for segregating the variants in affected families, as well as functional studies in cellular and animal models to comprehend the repercussion of genetic variants.

Biomarkers

Precision Medicine involves several strategies, one of which is the identification of new biomarkers for cardiomyopathies that have a favorable correlation with prognosis and allow therapeutic monitoring. These biomarkers can be of different natures, and diagnostic imaging tools have played a prominent role in this field. New magnetic resonance imaging, echocardiography, and nuclear medicine techniques have allowed more accurate assessment of cardiomyopathies. Examples include the quantification and topography of fibrosis by delayed enhancement, the evaluation of myocardial composition and extracellular volume by T1 mapping in magnetic resonance imaging, earlier detection of alterations in systolic function with longitudinal strain in echocardiography, and the development of new radiopharmaceuticals with potential in nuclear medicine, such as fibroblast activation proteins, which have demonstrated potential in the assessment of myocardial fibrosis formation.¹⁸⁻²⁰

In addition, wearables, such as smartwatches, adhesive patches, and other implantable devices, have gained importance as biomarkers, as they allow real-time assessment of several markers of physiological functions, such as cardiac rhythm, heart rate, blood pressure, plethysmography, oximetry, temperature, and others. They also make it possible to analyze patient behavior in an integrated manner over a long period of time. These devices, combined with artificial intelligence tools, allow earlier diagnosis of acute events and more precise interventions.²¹ Recent examples range from the Apple Watch to more complex devices such as CardioMEMS and ZOLL HFMS, which have shown benefits in prospective clinical studies.^{22,23}

Another promising group of biomarkers is derived from multiomic assessment of patients. These strategies, which use next-generation sequencing and mass spectrometry, make it possible to assess an immense number of molecules in different biological materials, such as serum and tissues. These data, analyzed using bioinformatics tools, can assist in understanding the pathophysiology of cardiomyopathies and establish new therapeutic targets and useful biomarkers in clinical practice.²⁴ An example of this type of biomarker is the MasSpec Pen, developed by a Brazilian researcher, which assists tissue assessment in different types of tumors.²⁵

Therapies

The treatment of cardiomyopathies has been advancing with the development of new molecular technologies and targeted therapies. A notable example is patisiran, a small interfering RNA (siRNA)-based treatment approved by the United States Food and Drug Administration (FDA) in 2018 to treat ATTR.²⁶ In the 1990s, Fire and Mello described RNA interference, for which they received the Nobel Prize in Physiology and Medicine in 2006, but it was only in 2018 that patisiran, the first drug of its kind, was approved by the FDA.²⁷ Although translating these new technologies into concrete clinical benefits is a challenge that requires time and investment, these advances emphasize the potential of new therapeutic methodologies. Other targeted treatments already approved for clinical use include mavacamten, an allosteric cardiac myosin inhibitor for patients with obstructive hypertrophic cardiomyopathy.²⁸

A promising therapeutic technology is cell therapy, which has already shown benefits in preliminary clinical studies in patients with ischemic heart disease, using mesenchymal stem cells.²⁹⁻³¹ The improvement of cell expansion and differentiation techniques may allow for more widespread use of these technologies. Induced pluripotent stem cell-derived cardiomyocytes are a possibility that may benefit patients with cardiomyopathies with heart failure, given that low rates of cell regeneration of adult cardiomyocytes prevent repopulation in areas of myocardial fibrosis, leading to contractile dysfunction and arrhythmogenic substrate.³²

The emergence of CRISPR-Cas9 technology has made gene editing feasible and controlled in cell and animal models, as demonstrated by Jennifer Doudna and Emmanuelle Charpentier, who received the Nobel Prize in Physiology and Medicine in 2020.³³ Given the important genetic substrate of most cardiomyopathies, gene therapy may have curative potential, especially if used in the preclinical phases of the diseases. In 2023, the FDA approved the first treatment based on CRISPR-Cas9, exagamglogene autotemcel, indicated for patients with sickle cell anemia, paving the way for the development of this technique in several areas of medicine, as occurred with siRNA.

Barriers

Precision Medicine is a promising approach in medical practice, but its incorporation into the Brazilian Unified Health System (SUS, acronym in Portuguese) faces several barriers. One of the main difficulties is the high cost of genetic tests, molecular phenotyping strategies, and new targeted treatments. Although there are prospects for reducing some of these costs, as has been the case with next-generation sequencing, large-scale studies are still required to demonstrate their effectiveness and cost-benefit ratio.

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In Brazil, Precision Medicine strategies are still restricted to highly specialized centers, with a strong academic-scientific bias. Moreover, professional training is another important barrier to its dissemination. Many health professionals have not received adequate training to handle genetic and molecular tools, and considerable effort in continuing education is needed to disseminate knowledge about the technology.

Another important difficulty is logistics. Brazil faces significant regional inequalities in the distribution of resources, which makes it difficult to incorporate Precision Medicine strategies within the scope of the SUS. It is necessary to establish well-defined flows to conduct family genetic screening in healthy individuals who are in primary care. Pilot projects can help identify these logistical barriers and propose viable and sustainable solutions.

Perspectives

There are exciting prospects for advancing Precision Medicine in the treatment of cardiomyopathies. With the growing integration of techniques and tools in clinical practice, it is believed that the resources already available, such as genetic testing, will become increasingly widespread, while other technologies in the process of translation become more accessible.

In order for these technologies to be successfully implemented, it is crucial that scientific progress be accompanied by professional training, optimization of clinical management, and ethical and legal supervision. Only then can we ensure that Precision Medicine reaches its full potential in improving the treatment of cardiomyopathies.

Author Contributions

Conception and design of the research: Giugni FR, Krieger JE; Writing of the manuscript: Giugni FR; Critical revision of the manuscript for important intellectual content: Krieger JE.

Potential conflict of interest

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

Sources of funding

There were no external funding sources for this study.

Study association

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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