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PERSPECTIVE

Genomic Medicine: Perspective of the Challenges for the Implementation of Preventive, Predictive, and Personalized Medicine in Latin America

Marcela Perenguez[1], Diana Ramírez-Montaño[2,*], Estephania Candelo[3], Hector Echavarria[4] and Alejandro De La Torre[5]

[1]*Genomic Medicine and Genetic Unit, Clinica Imbanaco Grupo QuirónSalud, Department of Biological Sciences, Bioprocesses and Biotechnology, School of Engineering, Design and Applied Sciences, Universidad Icesi, Cali, Colombia;* [2]*Genomic Medicine and Genetics Unit, Department of Medical Genetics, Biotecnología y Genética SAS, Clinica Imbanaco Grupo QuirónSalud, Colombia, Colombia;* [3]*Center for Rare Diseases and Congenital Anomalies (CIACER), Clinical Research Center, Universidad Icesi, Colombia, Fundación Valle del Lili, Cali, Colombia;* [4]*Genomic and Genetic Medicine Unit, Clinica Imbanaco Grupo QuirónSalud, Colombia;* [5]*Scientific Direction, Clínica Imbanaco Grupo QuironSalud, Cali, Colombia*

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Abstract: Genomic information plays an essential role in personalized medicine, with the main objective of determining risk and predisposition to disease, as well as guiding diagnosis, selection, and prioritization of therapeutic options, and even predicting prognosis. Research in the second half of the 20th century allowed genomics to move from the laboratory to clinical practice. The Human Genome Project showed the structure of the genome, the genes, and several of their regulatory pathways, which allowed obtaining exact knowledge about the molecular origin of a growing number of diseases and the development of next-generation sequencing technologies. In the second decade of the 21st century, the decrease in testing costs has allowed genomic medicine to begin to be applied in hospital institutions and outpatient services with a positive impact on public health. However, it has been evidenced that these potential benefits have not been experienced equitably throughout the world. This commentary explores the main challenges and obstacles to the implementation of genomic medicine services in order to expand their use as part of clinical practice in the Latin American context. Finally, six main barriers have been identified: i) high costs and poor access, ii) lack of trained personnel in the genomic field, iii) negative personal and social beliefs, iv) lack of representation of Latin American populations in genomic databases, v) scarce evidence of impact on clinical practice, and vi) lack of understanding of genomic test results by patients and clinicians.

Keywords: Genomic medicine, personalized medicine, genetic testing, barriers, genomic data, predisposition to disease.

1. INTRODUCTION

Genomic medicine is a growing discipline that involves the use of a person's genomic information as part of their clinical care, with the main objective of determining risk and predisposition to disease, as well as guiding diagnosis, selection, and prioritization of therapeutic options, and even predicting prognosis [1, 2]. The option to offer targeted treatments and the possibility of developing new therapies based on advances in genomic sequencing have given way to what is known as Personalized Medicine (PM) and, more recently, to precision medicine, which has been recognized as the "medicine of the future" [3].

The growth of this discipline began with the results obtained from the Human Genome Project (HGP), which lasted 13 years and carried out the complete mapping of DNA, providing answers to questions regarding the origin and prediction of some diseases, thereby transforming healthcare [2, 4]. This has led governments in developed countries to increasingly

*Address correspondence to this author at the Genomic Medicine and Genetics Unit, Department of Medical Genetics, Biotecnología y Genética SAS, Clinica Imbanaco Grupo QuirónSalud, Colombia, Colombia; E-mail: diana.ramirezm@quironsalud.com

invest in genomic medicine, initially focusing on rare diseases and cancer, with the long-term intention of incorporating genomic information into a new data ecology to support the development of more precise medical treatments, better patient stratification, and more efficient and cost-effective use of healthcare resources [5, 6].

Currently, genomic sequencing is conceived as a tool to improve diagnostic rates for more than 7,000 individually rare, but collectively common, monogenic diseases that affect more than 5% of the population in high-income countries [7, 8]. Sequencing results vary by disease, with some achieving diagnostic yields of 25% to 50%, including intellectual disability, eye disease, and, in selected cases, acute illness, such as in children hospitalized in intensive care units [9]. Additionally, in oncology, genomic profiling of tumors has become part of the clinical routine to predict response to therapies, improve interpretation of the tumor genome, and identify clinically relevant variants [5]. Even since the COVID-19 pandemic, research is underway to gather genomic information to understand the severity of different clinical scenarios, hoping to elucidate the molecular susceptibility factors for the severe outcomes observed in some individuals [10, 11].

Today, genomic information together with medical image analysis is playing an essential role in personalized medicine for patients with cancer, with an emerging field called radiogenomics, providing prognostic models for gene expressions or biomarkers based on imaging features [12-14]. Thus, genomic medicine is also taking advantage of artificial intelligence in order to help clinicians change their traditional approach by combining omics data with clinicopathological patterns to serve as a non-invasive method for selecting personalized management strategies [15, 16]. Although globally, the costs of sequencing technologies have decreased significantly in the last decade, their transition into routine clinical practice has been slow and seen as a privilege of high-income countries [17], mostly because knowledge in genomics is still limited for clinicians, patients, and the general population. In the Latin American context, where 80% of the countries are considered developing countries, the approach to diseases from a genomic medicine perspective has been even slower due to economic conditions [18-20]. For example, although universal screening for mutations in the BRCA1 and BRCA2 genes is recommended for breast cancer patients, in the region, it has been identified that only 15% of cases are actually screened, which represents a disparity compared to other regions of the world [21]. Additionally, within the United States, an underrepresentation of the Latino population has also been reported in precision medicine-based research studies to evaluate potential therapies for breast, prostate, lung, and colorectal cancers [21]. Therefore, in this commentary, we sought to describe the main challenges and obstacles to the implementation of genomic medicine services, as well as expand their use as part of clinical practice in the region.

2. GENOMIC MEDICINE WITHIN CLINICAL PRACTICE

The diagnosis of diseases under the conventional approach is based on the symptomatology and clinical manifestations of the disease, supported by diagnostic tests, which, in most cases, do not reveal the cause and only lead to the resolution of the immediate symptoms. In contrast, genomic medicine seeks to identify the origin or existing genetic risk of multiple diseases that can affect an individual and his/her family, even in the absence of clinical manifestations. As shown in Fig. (**1**), the implementation of genomic medicine in clinical practice begins with genomic screening to identify individuals at high genetic risk for health conditions based on genetic variants in order to promote primary care and prevention actions. Currently, there are two types of genetic testing: clinical or Direct-to-consumer (DTC) (Fig. **1**). Clinical tests are aimed at identifying pathogenic variants that may explain the development of a disease or condition, generating knowledge that allows the assessment of future health risks through the analysis of DNA that can be studied by Next-generation Sequencing (NGS) studies for specific genes, Whole Exome Sequencing (WES), or Whole Genome Sequencing (WGS) [22, 23]. Generally, clinical tests are performed as part of medical conduct, contrary to what happens with DTCs, and can be requested directly by an individual only to obtain general genetic information without necessarily involving a physician or active symptomatology [24, 25]. Examples of companies offering DTC kits are 23andMe, AncestryDNA, National Geographic Geno 2.0, My107 Heritage DNA, Habit, Pheramor, and DNAFit (Fig. **1**). However, these tests have been introduced primarily by entertainment genetics services and are not related to medicine.

The value of genomic medicine lies in the interpretation and use of genetic information, which means that the results of DTC tests in the absence of an expert can lead to misinterpretations or wrong decision-making. The clinical impact of DTC tests is not yet validated, and they should not be considered diagnostic or clinical predictive tests that contribute to the implementation of genomic medicine in our countries. The correct interpretation of genetic tests is oriented toward the identification of pathogenic variants that can explain the health-disease process, which makes it possible to classify them as pathogenic, benign, or of uncertain significance [26]. This grouping should be done taking into account the frequency of variants in

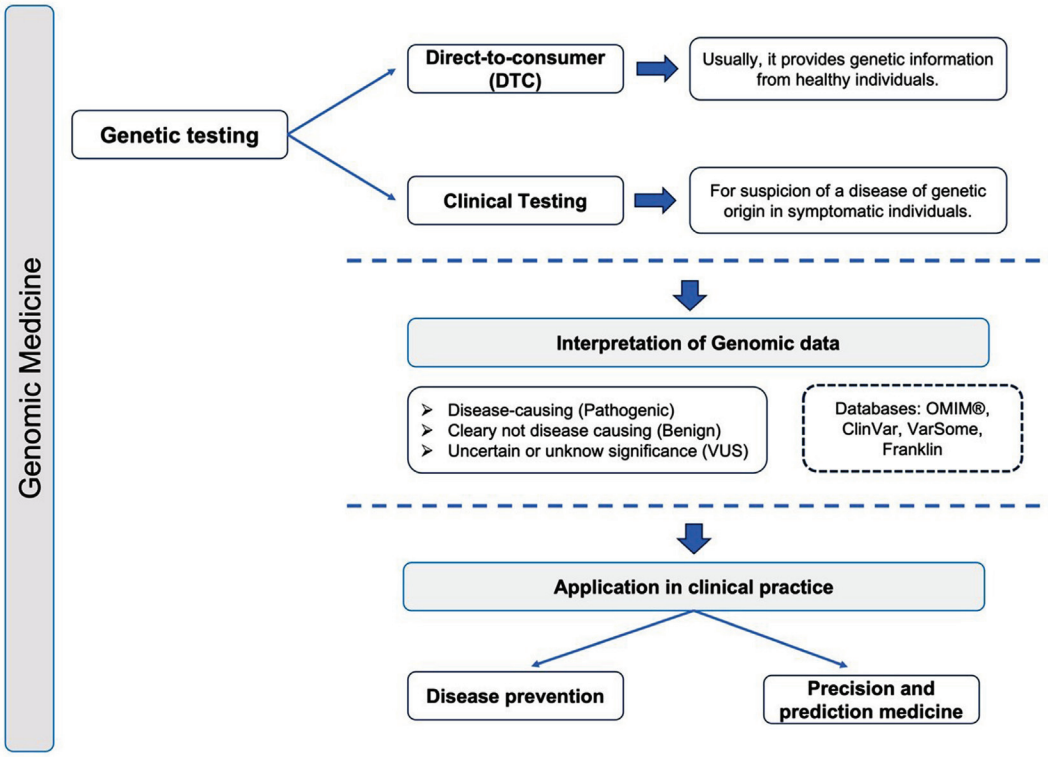

Fig. (1). Description of genomic medicine in clinical practice. Source: Own elaboration. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the population and current evidence, so there are databases or tools that help discriminate clinically relevant variants from those that are not, such as gnomAD (Genome Aggregation Database, https://gnomad.broadinstitute.org), ClinGen (http://clinicalgenome.org), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), VarSome (http://varsome.com), or Franklin (http:// franklin.genoox.com).

The clinical utility of the results, however, may depend on the perspective of the treating physician, who, in patients with a given pathology (*e.g.*, oncologic pathologies), may take a precision medicine approach to identify therapies that may offer greater benefit based on genetic information, characteristics of the individual, as well as the identification of other biomarkers, moving away from the "one-size-fits-all" approach [27]. Another possible use of genomic medicine is to apply the results of genetic testing from a preventive and predictive perspective. This can generate prevention strategies to mitigate an individual's genetic risk or susceptibility to the development or recurrence of a particular disease (Fig. **1**). This alternative could prove to be cost-effective over time by reducing the risk of onset and allowing early diagnosis and treatment, which may result in minimal sequelae. However, at present, this use is not frequent due to scarce evidence reported [28].

3. CHALLENGES AND OBSTACLES TO IMPLEMENTATION IN THE LATIN AMERICAN CONTEXT

The translation of genomic medicine into routine clinical practice has been a gradual and sustained process, mainly in the diagnosis, stratification, and treatment of patients with oncological diseases or in the context of neonatal screening [7]. However, most of these learnings have come from studies conducted in high-income countries, such as the United States (48%) and England (16%) [29]. In Latin America, the arrival of COVID-19 highlighted the poor technological capacity of the region. According to the Pan American Health Organization (PAHO), at the beginning of the pandemic, only Brazil and Chile had public laboratories equipped with state-of-the-art technology to perform genomic sequencing of the virus, so the performance of more complex local tests, such as NGS, WES, or WGS, was and continues to be limited, mainly in government health institutions.

In search of overcoming the paradigm of conventional medicine and giving way to personalized and preventive medicine, the importance of making progress in this field has been recognized. Therefore, in different countries, such as Mexico, Brazil, Argentina, Chile, and Colombia, the creation of education programs in genomic medicine, molecular biology, and clinical healthcare services specialized in genomic

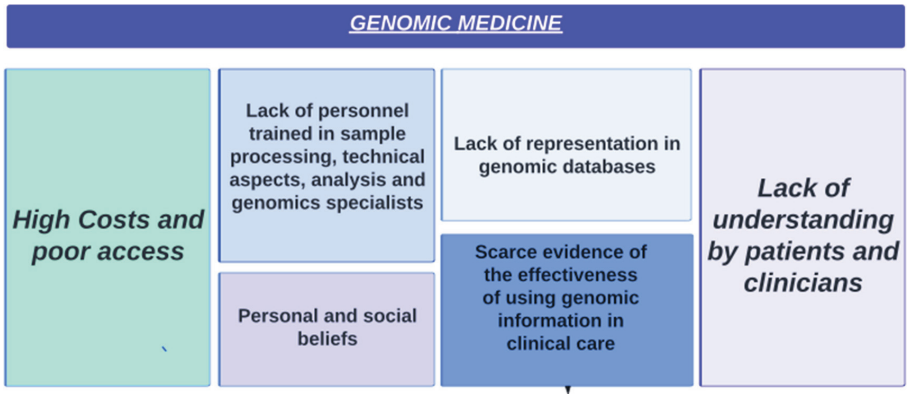

Fig. (2). Barriers to the implementation of genomic medicine in Latin America. Source: Own elaboration. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

medicine has been promoted [30]. Additionally, due to the low representation of the Latin population (~1%) in databases and epidemiological studies of genetic variants in the world [48], an initiative has arisen to create a platform that only includes genetic information from Latin American individuals called GLAD (Genetics of Latin American Diversity), to allow a better understanding of genetic diversity and favor the application of personalized medicine [31].

The above initiatives have also identified significant barriers to the growth and implementation of genomic and personalized medicine in the region, which are detailed in Fig. (**2**). The high cost of genetic testing has been the main barrier, which has been attributed to the low number of tests performed, the lack of local laboratories, and the absence of laws regulating testing costs. Another relevant aspect is that most genetic tests are not included in the health coverage, which does not allow adequate reimbursement by insurers and forces patients to assume the costs of these tests, making them a privilege of a few and reducing the opportunity for access to the general population. The high costs are also explained by the lack of trained personnel in the region and the absence of the necessary technological resources that prevent the creation of local laboratories for analysis, forcing the use of international services, thereby raising costs and delaying the timing of results due to shipping times.

On the other hand, because genomic and personalized medicine is a new field of knowledge, so far, it has not been possible to determine its real impact in the clinic as there exist inconclusive findings regarding its cost-effectiveness [29, 32, 33], which has generated skepticism among specialists in different areas. Its effectiveness, however, is currently recognized in early diagnosis of rare or orphan diseases in neonates and children, so its use is encouraged in this age group [34-36]. The lack of confidence of healthcare personnel in genomic medicine is also reflected in the poor knowledge that patients and the general population have about its potential benefits and implementation, causing it to be underestimated as part of comprehensive care. Social and individual beliefs have also generated rejection on the part of patients due to the fear of knowing if they have a genetic susceptibility or risk of developing a disease, which could even generate recrimination or feelings of guilt among family members. The perception that the interpretation and implementation of genetic test results are difficult has also been a cause of rejection among specialists. This highlights the need to incorporate multidisciplinary and interdisciplinary services within hospital institutions that allow the implementation of liaison services with genetics specialists to guide the performance of clinical tests, interpretations, and their translation to patient care.

CONCLUSION

Currently, genomic medicine and PM have diverse applications in a wide range of complex diseases in which inter-patient and intra-patient variability has a major impact on diagnosis, treatment, and prognosis, such as breast cancer, lung cancer, hepatitis C, or myocardial infarction [37]. Several studies have revealed that molecular characterization of Latin American populations may differ from that observed in European or North American populations [38, 39]. In the Latin American region, the lack of knowledge in the field of genomics, the underutilization of the services already offered, the lack of massification of genetic testing, as well as the scarce number of professionals with expertise in health institutions, are priority aspects that must be addressed in order to broaden the application of genomic medicine in clinical practice.

There is a clear need for governments to support health systems in giving the importance that the applicability of genomic medicine deserves, concentrating efforts on reducing the high costs to health systems

aimed at treating diseases that can be addressed from a preventive approach at the individual, family, and population levels. To facilitate the rapid translation of genetic test results, the capacity of the healthcare system needs to be increased, especially in laboratory and genetic services, including human personnel. It is also necessary to focus on educating health professionals by introducing continuing education programs in genomics both at the level of health faculties and clinical institutions. This is also relevant from ethical and legal aspects of genomic medicine because it is important to understand the true scope of the application of technologies, such as WGS, without generating unrealistic expectations among patients [40, 41]. For example, in the case of complex or polygenic conditions of a multifactorial cause involving environmental or lifestyle factors, it is paramount to inform the patient that genomic data will only provide risk information that can be managed from a preventive medicine approach [7, 37].

A paradigm change in medical practice is currently taking place with the goal of addressing a disease by finding the unique fingerprint that the disease imprints on a person. As far as a customized data-driven approach is concerned, it can be made possible by the unification of multi-omics methods, featuring each patient individually, and this can further allow the real implementation of PM [42, 43]. Furthermore, from the perspective of real, Personalized, Predictive, and Preventative Medicine (PPPM), Artificial Intelligence (AI) strategies present a significant potential for customized and early disease detection. It is crucial that AI-based models are thoroughly evaluated in order to implement PPPM in clinical settings [37]. Current research indicates that in terms of diagnosing syndromes, facial analysis techniques, on par with qualified therapists and mathematic models that integrate the knowledge about the hallmark of cancer, are currently underway to describe breast cancer progression [42, 43] Additionally, the discovery of diverse biomarkers has been improved for diagnostic, prognostic, and selection systems for developing PM [44]. For example, DNA from chromosome 21 is counted in prenatal blood as part of the Down's syndrome biomarker screening. Examples of predictive and prognostic biomarkers in current use are genomic tools for somatic analysis of diverse tumors of breast, prostate, and ovarian origin, such as BluePrint®, MammaPrint®, OncoTypDx, and Epidermal Growth Factor Receptor (EGFR) in the case of advanced non-small cell lung cancer [45].

Considering that genetic data from the Latin American region in population-based studies (GWAS) are limited, collaborative initiatives are needed to understand pharmacogenetics. For example, in Chile, as described by Olloquequi *et al.* [39], a successful public-private partnership has helped to determine pharmacogenetic variants specific to Chileans, including the rural population and involving ancestral variability [39]. It is widely known that pharmacogenetic variants and responses to medications, particularly in underrepresented populations, are generally overlooked and ignored, although they constitute a key factor for the development of personalized medicine and its implementation [46]. This type of initiative reveals the importance of determining the differences in genetic variants in our populations and shows the opportunities to reduce the gaps in the knowledge of genomic variation in our countries, the differences with other populations, and their true impact at the clinical level.

Collaborative initiatives are not foreign to other underrepresented population groups. A recent study in the Russian population showed the results of precision medicine initiatives [47]. This study promoted the construction of a mutational profile for pancreatic cancer patients based on whole exome sequencing of 40 somatic tissue samples. The results evidenced differences with respect to findings in other populations, which could, in the future, guide the development of new targeted drugs, impacting the survival rates of hopeless patient groups with certainly limited therapeutic alternatives. This may further open up new opportunities for the application of personalized medicine.

This article has been generated from the knowledge gained during the implementation of a genomic medicine unit in a hospital located in Cali, Colombia. This unit, in addition to providing traditional genetic and genomic services, offers advice to patients. Likewise, it has been working to train doctors and patients about the benefits of genetics and personalized medicine and makes alliances with universities to carry out research.

The progressive expansion of services, education in genomics, research on clinical genetics, and the acquisition of genetic diagnostic equipment are elements that could make the application of genomic medicine a reality in the Latin American context. At this point, it is also necessary for the countries of the region to collaborate to improve current financing and implement common strengthening strategies in order to facilitate access to treatments and new technologies due to the similarity in economic, social, and health aspects among Latin American countries.

AUTHORS' CONTRIBUTIONS

M.P.: Writing–original draft. D.R.-M.: Writing–review and editing. E.C.: Writing–review and editing. H.E.: Writing–review and editing. A.T.: Writing–review and editing.

LIST OF ABBREVIATIONS

AI = Artificial Intelligence

DTC = Direct-to-Consumer

EGFR = Epidermal Growth Factor Receptor

HGP = Human Genome Project

NGS = Next-Generation Sequencing

PAHO = Pan American Health Organization

PM = Personalized Medicine

PPPM = Predictive, and Preventative Medicine

WES = Whole Exome Sequencing

WGS = Whole Genome Sequencing

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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