

MOLECULAR DIAGNOSIS OF GENETIC DISEASES IN THE ERA OF GENOMIC MEDICINE: TECHNICAL CHALLENGES, GENETIC COUNSELING, AND THE (DE)VALUATION OF THE MEDICAL PROFESSIONAL IN THE CONTEMPORARY BRAZILIAN CONTEXT

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Abstract

Over the past two decades, Genomic Medicine has become one of the most transformative pillars of contemporary clinical practice, redefining diagnostic, therapeutic, and preventive paradigms for diseases of genetic origin. This article aims to discuss, in light of current scientific literature, the molecular diagnostic protocols and techniques used to characterize genetic diseases, with emphasis on contemporary molecular biology methods applied to carrier detection, prenatal diagnosis, and genetic counseling. This is a qualitative narrative literature review based on Brazilian and international scientific publications, most of which were published during the past decade. The findings show that, despite major technological advances, such as next-generation sequencing, chromosomal microarrays, and digital PCR platforms, the effectiveness of Genomic Medicine in Brazil remains contingent upon structural, economic, and, above all, human factors. Particularly noteworthy is the growing devaluation of medical professionals,

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especially medical geneticists, whose work is indispensable to translating molecular knowledge into high-quality clinical care. It is concluded that the full integration of genomics into Brazilian public health depends not only on technological improvement but also on effective policies for the recognition, continuing education, and retention of specialized medical professionals. Without such policies, inequities in access to genetic diagnosis and counseling may widen.

Keywords: Genetic Counseling, Genetic Diseases, Genomic Medicine, Molecular Diagnosis, Professional Recognition of Medical Professionals.

INTRODUCTION

The rapid advancement of the omics sciences, including genomics, transcriptomics, proteomics, and metabolomics, has irreversibly reshaped the foundations of contemporary medical practice. In this context, what is known as Genomic Medicine has emerged not as a field isolated from classical genetics, but as an epistemological reformulation of clinical practice as a whole, in which diagnosis, prognosis, and treatment are understood in light of each patient's individual molecular architecture (Green et al., 2020; Manolio et al., 2019).

Since the completion of human genome sequencing in the early 2000s and its subsequent technological democratization through next-generation sequencing (NGS) platforms, there has been an exponential increase in diagnostic capacity for diseases of genetic etiology, which had previously been limited to presumptive clinical diagnoses or low-resolution cytogenetic techniques (Rehm & Green, 2021).

The molecular characterization of genetic diseases is no longer an ancillary tool and has become, in numerous conditions, the only method capable of establishing a definitive diagnosis. This is particularly true of rare diseases, in which phenotypic overlap among different syndromes frequently precludes differentiation based solely on clinical findings (Boycott et al., 2019).

It is estimated that more than seven thousand rare diseases have been described, approximately 80% of which have an identifiable genetic origin and collectively affect between 6% and 8% of the global population (Nguengang Wakap et al., 2020). In Brazil, the National Policy for Comprehensive Care for People with Rare Diseases (Política Nacional de Atenção Integral às Pessoas com Doenças Raras) (Brasil, 2014; Brasil, 2023) formally recognizes the magnitude of this epidemiological burden and reinforces the need to establish specialized healthcare networks, within which Medical Genetics Services play a central role.

Within this context, molecular genetics laboratories affiliated with university hospitals and public referral services perform a strategic function in the continuum of care. They enable not only diagnostic confirmation in clinically suspected cases but also the extension of molecular testing to asymptomatic relatives through carrier detection and to pregnant women at increased reproductive risk through molecular prenatal diagnosis (Skotko & Kishnani, 2022).

These strategies make more accurate genetic counseling possible, based on more precise estimates of recurrence risk, representing a substantial improvement over exclusively probabilistic models based on pedigrees.

However, the integration of these technologies into healthcare practice is neither neutral nor automatic. It depends decisively on the presence of properly trained medical professionals, including clinical geneticists, molecular pathologists, obstetricians trained in fetal medicine, pediatricians, and other specialists, who are capable of interpreting complex molecular findings, correlating them with the clinical presentation, and translating them into therapeutic decisions and ethically responsible guidance for families (Sanderson et al., 2021).

Paradoxically, contemporary Brazil has witnessed a growing process of devaluation of the medical profession, reflected in increasingly precarious employment arrangements, the longstanding inadequacy of the reimbursement rates paid by the Unified Health System (Sistema Único de Saúde—SUS) and supplementary health insurance plans, excessive clinical workloads, and the symbolic erosion of the

profession's standing in public and media discourse (Scheffer et al., 2023; Machado & Oliveira, 2022).

This phenomenon is particularly critical in specialties with limited immediate economic visibility, such as medical genetics, which requires lengthy training and a high degree of technical specialization while offering comparatively limited financial returns relative to more procedure-intensive specialties.

Against this backdrop, this article presents an up-to-date and contextualized discussion of the technical foundations of the molecular diagnosis of genetic diseases, critically linking them to the recognition, or devaluation, of medical professionals as indispensable yet frequently overlooked elements in the system that underpins the effectiveness of Genomic Medicine.

It is argued that technology alone cannot produce clinical and social impact without qualified medical mediation. Accordingly, policies intended to strengthen clinical genomics must necessarily incorporate robust strategies for professional recognition, or they risk exacerbating existing inequalities in access to genetic diagnosis in Brazil.

METHODOLOGY

This is a qualitative, exploratory, and descriptive study structured as a narrative literature review, a method widely recognized as appropriate for broad and contextualized discussions of complex, multifaceted topics in which technical and scientific foundations are integrated with critical social, ethical, and organizational reflections (Rother, 2007; Cronin & George, 2023).

This article was developed according to the following methodological stages:

a) Definition of the guiding question: The study sought to address the following central question:

How have contemporary advances in the molecular diagnosis of genetic diseases affected the practice of genetic counseling in Brazil, and to what extent does the devaluation of medical professionals compromise the effectiveness and equity of this process?

b) Literature search: Searches were conducted in PubMed/MEDLINE, the Scientific Electronic Library Online (SciELO), Google Scholar, the Virtual Health Library (Biblioteca Virtual em

Saúde—BVS), and institutional journals associated with Brazilian and international medical genetics societies, including the Brazilian Society of Medical Genetics and Genomics (Sociedade Brasileira de Genética Médica e Genômica—SBGM), the American College of Medical Genetics and Genomics (ACMG), and the European Society of Human Genetics (ESHG). Priority was given to publications issued between 2018 and 2024 to ensure that the technical and conceptual discussions presented were current, without precluding the selective inclusion of classic references of structural and historical importance that were essential to understanding the field's development.

- c) Inclusion criteria: Original articles, systematic and narrative reviews, clinical guidelines issued by specialty societies, government regulatory documents, and chapters from major reference works in medical and molecular genetics were considered. All materials were written in Portuguese, English, or Spanish and were available in full text.
- d) Exclusion criteria: Materials that had not undergone peer review, conference abstracts without sufficient methodological detail, and publications that were redundant or outdated in light of more recent evidence were excluded.
- e) Analysis and synthesis: The selected material underwent analytical reading, thematic categorization, and critical synthesis. The content was organized into central thematic axes covering the foundations of Genomic Medicine, molecular diagnostic techniques, genetic counseling, and the human and professional dimensions of clinical genetics. These axes structure the development of this article.

Because this was a narrative literature review rather than research involving human participants, submission to a Research Ethics Committee was not required, in accordance with National Health Council Resolution No. 510/2016 (Brasil, 2016). The study's ethical commitment therefore lies in its faithful interpretation of the sources consulted and the transparency of the methodological and analytical choices adopted.

DEVELOPMENT

GENOMIC MEDICINE: FOUNDATIONS, DEVELOPMENT, AND THE RECONFIGURATION OF CLINICAL PRACTICE

Genomic Medicine may be defined as the field of medical practice that uses information derived from the individual genome, and, more broadly, from its structural, epigenetic, and functional variants, to inform clinical decisions concerning the prevention, diagnosis, and treatment of health conditions (Green et al., 2020).

It differs from traditional medical genetics, which focuses more heavily on the study of individual genes and classical Mendelian disorders, through its systemic and integrative approach. This approach encompasses conditions ranging from rare monogenic variants to the polygenic architecture of common diseases such as diabetes, cardiovascular disease, and various types of cancer (Manolio et al., 2019).

The foundational milestone of this field was the completion of the Human Genome Project in 2003, which enabled the complete mapping of the human genome's nucleotide sequence (Lander, 2011).

However, the routine application of genomics to clinical practice became feasible only with the development and subsequent widespread adoption of next-generation sequencing technologies beginning in the second decade of the twenty-first century, owing to the dramatic reductions in sequencing costs and turnaround times (Rehm & Green, 2021).

According to data from the National Human Genome Research Institute, the cost of sequencing a complete human genome, which exceeded USD 100 million in 2001, had fallen to less than USD 1,000 in large-scale sequencing settings by 2015 and has continued on a downward trajectory (Wetterstrand, 2023).

This reduction in cost enabled the progressive integration of genomics into different levels of healthcare, from primary care to highly specialized services, substantially changing the care model for genetic conditions.

Rehm and Green (2021) identify four major areas of application around which contemporary Genomic Medicine is organized: (i) the molecular diagnosis of Mendelian and rare diseases; (ii) population screening and carrier detection; (iii) pharmacogenomics, involving individualized therapeutic adjustment; and (iv) oncogenomics, involving the molecular characterization of tumors for prognostic and therapeutic purposes.

In Brazil, the integration of Genomic Medicine into the Unified Health System has progressed unevenly and, at times, inadequately. It remains concentrated predominantly in university hospitals and regional referral centers, which serve as hubs for the dissemination of technical knowledge and the provision of specialized care (Horovitz et al., 2022).

The National Policy for Comprehensive Care in Clinical Genetics (Política Nacional de Atenção Integral em Genética Clínica), established by Ordinance No. 199/2014 and reformulated through subsequent regulations (Brasil, 2014; Brasil, 2023), sought to establish a national medical genetics referral network linking services at different levels of complexity.

Nevertheless, recent studies indicate that these services remain geographically concentrated in Brazil's South and Southeast, undermining equitable access to genetic diagnosis in historically underserved regions such as the North and Northeast (Horovitz et al., 2022; Zatz et al., 2021).

CONTEMPORARY TECHNIQUES FOR THE MOLECULAR DIAGNOSIS OF GENETIC DISEASES

The molecular characterization of genetic diseases is based on a diverse set of molecular biology techniques. The technique selected depends on the nature of the clinical suspicion, the type of genetic alteration expected, such as a single-nucleotide variant, deletion, duplication, repeat expansion, or complex structural rearrangement, and the health service's technological and financial resources.

- a) Polymerase Chain Reaction (PCR) and its contemporary variants: PCR remains a foundational technique in diagnostic molecular biology and is widely used to amplify specific genomic regions before sequence or fragment analysis.

Contemporary variants, such as real-time quantitative PCR (qPCR) and, more recently, digital PCR (dPCR), offer substantially greater sensitivity and precision. They enable, for example, the absolute quantification of gene copy number and the detection of variants with low allele frequencies, with growing relevance to oncogenomics and noninvasive prenatal testing (Cifuentes et al., 2023).

b) Next-Generation Sequencing (NGS): NGS revolutionized molecular diagnosis by enabling the simultaneous sequencing of multiple genes through multigene panels, the entire exome through Whole-Exome Sequencing (WES), or the entire genome through Whole-Genome Sequencing (WGS), within time and cost parameters compatible with clinical practice (Rehm & Green, 2021).

Recent multicenter studies show that exome or genome sequencing, when used as a first-line diagnostic strategy for rare diseases of undetermined etiology, achieves diagnostic yields between 30% and 50%. These rates are substantially higher than those obtained through traditional sequential, gene-by-gene testing approaches (Clark et al., 2018; Splinter et al., 2018; French et al., 2019).

In Brazil, initiatives such as the Rare Genomes Project (Projeto Genomas Raros) and population sequencing consortia have sought to expand access to these technologies, although their full integration into the SUS remains incipient (Zatz et al., 2021).

c) Chromosomal Microarray Analysis (CMA): Primarily indicated for the investigation of intellectual disability, autism spectrum disorders, and multiple congenital anomalies of undetermined etiology, this technique enables the detection of submicroscopic structural variants, including genomic deletions and duplications known as Copy Number Variants (CNVs), which cannot be identified through conventional karyotyping.

International guidelines, including those issued by the American College of Medical Genetics and Genomics (ACMG), recommend CMA as a first-line test for patients with syndromic or

nonsyndromic intellectual disability of undetermined cause. This has restricted the use of traditional karyotyping to more specific indications, such as suspected classical aneuploidies or balanced rearrangements (Miller et al., 2010; South et al., 2021).

In the prenatal context, CMA has been progressively incorporated into the investigation of fetal anomalies identified by ultrasonography, increasing the diagnostic yield compared with fetal karyotyping alone (Levy & Wapner, 2018).

- d) Sanger sequencing: Despite the expansion of NGS, Sanger sequencing remains methodologically relevant as a confirmatory technique, particularly for validating variants identified by high-throughput platforms and for the targeted testing of relatives for variants previously identified in the index case, known as cascade testing. It therefore represents an indispensable stage in the carrier-detection process (Rehm & Green, 2021).
- e) Techniques for detecting repeat expansions and epigenetic abnormalities: Disorders such as fragile X syndrome, spinocerebellar ataxias, and Huntington's disease, which are characterized by trinucleotide-repeat expansions, require specific methods, such as flanking-primer PCR and triplet-primed PCR, because conventional short-read NGS platforms have limited sensitivity for these alterations.

Similarly, disorders of epigenetic origin, such as Prader–Willi and Angelman syndromes, require specific methylation-analysis techniques, including Methylation-Specific PCR (MS-PCR) and Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) (Buiting et al., 2021).

- f) Noninvasive Prenatal Testing (NIPT) and fetal biopsies: The identification of circulating cell-free fetal DNA in maternal plasma enabled the development of Noninvasive Prenatal Testing (NIPT), a technique based on massively parallel sequencing that can screen for common fetal aneuploidies with high sensitivity and specificity. It reduces the need for invasive procedures

such as amniocentesis and chorionic villus sampling, which have traditionally been associated with a risk of pregnancy loss (Cifuentes et al., 2023).

It should be emphasized, however, that NIPT is a screening test rather than a definitive diagnostic test. Positive results must therefore be confirmed through invasive methods combined with conventional molecular or cytogenetic techniques (Skotko & Kishnani, 2022).

Taken together, these technologies reveal an increasingly sophisticated technical landscape. Paradoxically, this increases rather than reduces the need for specialized medical mediation, as the proliferation of diagnostic platforms requires professionals to judiciously select the most appropriate test for each clinical context and to competently interpret results that are often ambiguous. These include Variants of Uncertain Significance (VUS), which remain common even with the most advanced platforms (Richards et al., 2015; Rehm & Green, 2021).

CARRIER DETECTION, PRENATAL DIAGNOSIS, AND GENETIC COUNSELING: AN INSEPARABLE TRIAD

The detection of asymptomatic carriers of pathogenic variants is a central pillar of secondary prevention in medical genetics, particularly for autosomal recessive and X-linked disorders, in which heterozygous individuals do not manifest the phenotype but face a significant reproductive risk.

Carrier-screening programs, traditionally directed toward populations at increased risk, such as cystic fibrosis screening in certain ethnic groups or hemoglobinopathy screening in high-prevalence regions, have expanded in the genomic era to include Expanded Carrier Screening (ECS). These approaches can simultaneously screen for hundreds of recessive conditions using NGS multigene panels (Edwards et al., 2015; Sanderson et al., 2021).

In Brazil, a country characterized by extensive population admixture and a high frequency of consanguineous marriage in certain regions, carrier screening has particular epidemiological relevance. This is especially true given the high prevalence of diseases such as sickle cell anemia and other

hemoglobinopathies, screening for which has formed part of the National Newborn Screening Program (Programa Nacional de Triagem Neonatal) since 2001 (Brasil, 2016; Zatz et al., 2021).

However, the extension of such screening to the preconception or prenatal period using broader molecular approaches remains limited outside major urban centers.

Molecular prenatal diagnosis enables the identification of fetal genetic conditions at a point in pregnancy when families can make informed reproductive decisions. These may concern preparing for the birth of a child with special needs, considering fetal therapeutic interventions when available, or evaluating circumstances in which the termination of pregnancy is legally permitted under Brazilian law, notably in cases of anencephaly and other fetal conditions incompatible with extrauterine life (Brasil, STF, ADPF 54, 2012).

It is precisely at this point that genetic counseling proves indispensable. According to the definition established by the National Society of Genetic Counselors, genetic counseling is “the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease” (Resta et al., 2006; updated by Ormond et al., 2018).

This is an inherently relational process that cannot be reduced to the mere communication of laboratory results. It requires the professional, whether a medical geneticist or a genetic counselor when one is part of the team, to possess sophisticated communication skills, ethical sensitivity when addressing complex reproductive decisions, and the ability to translate probabilistic information into terms that families can understand while respecting their autonomy and values (Sanderson et al., 2021; Ormond et al., 2018).

The international literature emphatically shows that the absence of qualified genetic counseling is associated with adverse psychosocial outcomes, including anxiety, guilt, poorly informed reproductive decisions, and distrust of the healthcare system (Skotko & Kishnani, 2022). This reinforces the central argument of this article: no molecular technology, regardless of how advanced it may be, can replace

qualified human and professional mediation. This necessarily leads to a discussion of the recognition afforded to such professionals in Brazil.

THE (DE)VALUATION OF MEDICAL GENETICISTS: A STRUCTURAL BOTTLENECK IN BRAZILIAN GENOMIC MEDICINE

Although the technological developments described in the preceding sections suggest a promising outlook for Brazilian clinical genomics, the sustainability of this model is seriously threatened by a multifaceted process of devaluation affecting the medical profession. This is particularly evident in specialties characterized by relatively few procedures and a high degree of cognitive complexity, such as medical genetics.

Data from *Demografia Médica no Brasil 2023* [Medical Demographics in Brazil 2023] (Scheffer et al., 2023) show that medical genetics is among the specialties with the smallest absolute number of professionals in the country. These professionals are heavily concentrated in the states of São Paulo, Rio de Janeiro, and Rio Grande do Sul, with alarming disparities relative to other regions. In several states in the North and Northeast, there are estimated to be fewer than one medical geneticist per 500,000 inhabitants.

This shortage does not result solely from a lack of vocational interest. Rather, it is associated with structural determinants that are well documented in the literature on the medical profession in Brazil (Machado & Oliveira, 2022; Scheffer et al., 2023):

1. Longstanding inadequacy of remuneration: The reference reimbursement rates in the SUS Fee Schedule for clinical genetics consultations and procedures have, for decades, remained disconnected from the technical complexity and clinical time required. A genetic counseling consultation often takes between 60 and 90 minutes, yet is reimbursed at a level incompatible with the time and expertise involved.

2. Precarious employment arrangements and the absence of a structured career path: Most medical geneticists working within the SUS are employed under precarious contractual arrangements, without career plans, opportunities for professional progression, or stability equivalent to that available in other public-service careers. This compromises professional retention, particularly outside major urban centers (Machado & Oliveira, 2022).
3. Excessive workloads and burnout: The shortage of professionals places an excessive burden on the few geneticists in practice. This phenomenon has been widely described in the literature on physician burnout and directly affects the quality of clinical listening and the genetic counseling provided (Scheffer et al., 2023).
4. Symbolic lack of prestige and institutional invisibility: Unlike specialties with high technological and media visibility, medical genetics remains poorly understood by public administrators and society in general. This results in low budgetary priority and insufficient investment in medical residency and continuing education in the field (Horovitz et al., 2022).

This situation creates a structural paradox: Brazil invests, albeit insufficiently, in laboratory infrastructure and technological integration, as exemplified by population genomic sequencing consortia, but fails to ensure the training, retention, and recognition of the medical professionals capable of translating this investment into effective care.

As Sanderson et al. (2021) aptly summarize, “genomic technology without qualified genetic counseling is, at best, incomplete information; at worst, it is a source of psychological and decisional iatrogenic harm.”

The devaluation of medical geneticists should therefore be understood not as a matter of professional self-interest or a demand made by a particular occupational category, but as an issue of public health and social justice. Their scarcity directly exacerbates regional inequities in access to genetic diagnosis and counseling. Populations in Brazil’s North and Northeast, which have historically received

less healthcare coverage, remain those most adversely affected by this gap in care (Horovitz et al., 2022; Zatz et al., 2021).

FINAL CONSIDERATIONS

This review has shown that Genomic Medicine unequivocally represents a paradigmatic revolution in the diagnostic, preventive, and therapeutic approach to genetic diseases. It is supported by an increasingly sophisticated technical arsenal, ranging from next-generation sequencing and chromosomal microarray analysis to the various forms of polymerase chain reaction and noninvasive prenatal testing techniques.

These advances have significantly expanded the capacity to establish definitive diagnoses of rare diseases, detect asymptomatic carriers, and screen for fetal conditions, directly improving the quality and accuracy of the genetic counseling offered to Brazilian families.

However, the critical analysis developed throughout this article supports the conclusion that technological determinism, understood as the belief that advances in molecular platforms alone would be sufficient to guarantee equitable, high-quality care, represents an inadequate and potentially dangerous interpretation of the Brazilian context.

Technology alone cannot interpret variants of uncertain significance, conduct an ethically responsible genetic counseling process, provide support to families facing the distress of an adverse diagnosis, or coordinate the healthcare network required for a patient's longitudinal follow-up. All these functions remain, and must remain, the irreplaceable responsibility of properly trained and adequately valued medical professionals.

The growing devaluation of the medical profession in contemporary Brazil, reflected in inadequate remuneration, precarious employment arrangements, excessive clinical workloads, and symbolic lack of prestige, has a directly harmful effect on the effectiveness of Genomic Medicine when it affects specialties characterized by relatively few procedures and high cognitive complexity, such as

medical genetics. It undermines the field's capacity to translate technological progress into tangible clinical benefits distributed equitably across the population.

It is therefore recommended that public policies aimed at expanding clinical genomics within the Unified Health System inseparably incorporate robust strategies for professional recognition, including revisions to reimbursement schedules, the establishment of structured career paths, an expansion in the number of medical residency positions in genetics, incentives to retain professionals in underserved regions, and stronger institutional and symbolic recognition of the specialty.

Without such measures, Brazil faces a concrete risk of consolidating a two-tier system of Genomic Medicine: cutting-edge genomics, technologically comparable to that available in the world's most advanced centers, accessible to a minority of the population concentrated in major urban centers; and a vast majority of the Brazilian population excluded from this progress, not because of technological limitations, but because of the absence of qualified medical professionals capable of transforming that technology into genuine care.

Future quantitative studies employing longitudinal designs are recommended to measure more precisely the direct effects of the shortage of medical geneticists on clinical and psychosocial outcomes among Brazilian families affected by genetic diseases. Such evidence could provide a robust foundation for the formulation of more effective public policies in this strategically important area of national healthcare.

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