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Playing catching up: proceedings of the 1st Spanish conference on genomic medicine

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Abstract

On May 23-24, 2024, the 1st Spanish Conference on Genomic Medicine convened in Madrid, Spain. An international and multidisciplinary group of experts gathered to discuss the current state and prospects of genomic medicine in the Spanish-speaking world. There were 278 attendees from Latin America, US, UK, Germany, and Spain, and the topics covered included rare diseases, genome medicine in national health systems (NHS), artificial intelligence, and commercial development ventures. One particular area of attention was our still sketchy understanding of genome variants. This is evidenced by the fact that many diagnoses in rare diseases continue to yield odysseys that take years, with up to 50% of cases that may go undiagnosed. Since a lot of the genome remains to poorly understood, as new technologies such as long read sequencing become more ubiquitous and cheaper, it is expected that current gaps in genome references will improve. However, disparities within the NHS suggest that advancements do not necessarily rely on resources but the appropriate regulation and pathways for education of professionals being properly implemented. This is where Genomics England can be a clinical genomic implementation example for routine health care. Ethical challenges, including privacy, informed consent, equity, representation, and genetic discrimination, also require the need for robust legal frameworks and culturally sensitive practices. The future of genomics in Spanish-speaking countries depends on addressing all of these issues. By navigating these challenges responsibly, Spanish-speaking countries can harness the power of genomics to improve health outcomes and advance scientific knowledge, ensuring that the benefits of personalized medicine are realized in an inclusive and equitable manner.

Keywords

Genomic medicine. Bioinformatics. Artificial intelligence. Rare diseases. Hereditary cancer. Direct to consumer genetic testing. Clinical genomics. Infectious diseases.

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Introduction

The field of clinical genomics has experienced exponential growth since the first complete human genome was sequenced in 2001[1,2]. This achievement has catalyzed numerous advancements, helping identify the genetic basis of some diseases and paving the way for personalized medicine.

The 1st Spanish Congress on Genome Medicine was held on May 23-24, 2024, in Madrid, Spain. The Congress gathered an international and multidisciplinary group of experts to explore the future of genomic medicine in Spain, Latin America, and the Spanish-speaking world, which according to the current estimates encompasses over 580 million people[3], 7.6% of the world's population. The conference attracted 278 attendees from Europe and the Americas, from a total of 19 nations, underscoring the global interest and importance of these discussions. Figure 1 shows the breakdown of nationalities among attendees and their geographical distribution across the globe.

The conference proceedings covered a wide range of topics, reflecting the diverse interests and expertise of participants. Key discussions included the interpretation of genetic variants; the experiences of national genomic initiatives, such as those of Mexico, Colombia, and Peru; and the role of host genomics in infectious diseases that are endemic in such regions. Each of these areas presents unique challenges and opportunities for advancing genomic medicine globally.

Health care through genomic medicine: Embracing 4P medicine

Genomic medicine has transformed traditional health-care paradigms, shifting the focus from reactive treatment of diseases to proactive and predictive approaches. The concept of 4P medicine –predictive, preventive, personalized, and participative– has emerged as a guiding framework[4]. This approach aims to predict disease risk, prevent disease onset, tailor personalized treatments, and engage patients in their health-care journey. The integration of genomic data as part of a 4P approach into clinical practice holds the promise of more accurate diagnoses, targeted therapies, and improved patient outcomes[5].

However, the rapid pace of technological development in genomics presents significant challenges, particularly in translating these innovations into clinical practice. While tools for genetic and genomic analysis have advanced considerably, the implementation of these tools in health-care systems has lagged significantly[6-13]. Effective implementation of genome medicine requires of robust bioinformatic infrastructure and the appropriate coordination between hospitals, universities, and government to develop the appropriate framework with which to extract actionable insights from genomic information, enabling clinicians to make informed decisions[14,15]. Ethical considerations are paramount in this process. Issues such as informed consent, data privacy, equity, and the representativeness of genetic databases are critical to ensuring that genomic medicine is implemented in a manner that respects patient rights and promotes equitable access to its benefits[16-19].

In the following sections, we delve into these topics, beginning with the challenges of variant interpretation, which remains a significant bottleneck in clinical genomics. We then explore the insights gained from national health systems (NHS) from across several countries. Finally, our perspectives in genomics of Latin America and Spain provide a comparative view for how different countries are adopting and integrating genomic medicine at different pace.

Critical challenges in clinical genomics

One of the critical challenges in clinical genomics is the interpretation of genetic variants[20-26]. Despite significant advancements in sequencing technologies, the clinical utility of genomic data remains constrained by our ability to accurately interpret genetic variants. This is a bottleneck that has profound implications for the implementation of genomic medicine, especially when it pertains to screening of healthy patients with no clear phenotype to which associate a genetic trait. This is mostly because while many variants can be classified based on established databases and previous studies, a substantial number remains ambiguous[27-29]. We call these variants of unknown significance. They pose a particular challenge as they cannot be definitively linked to disease without further evidence, which is yet to be produced.

The interpretation of genetic variants relies heavily on databases such as ClinVar[30], dbSNP[31], and the Human Gene Mutation Database[32]. The process of interpretation of variants, however, is still not standardized, and although the American College of Medical Genetics and Genomics has established guidelines on interpretation of genomic variants[33], these guidelines are not exhaustive, and the criteria can sometimes be

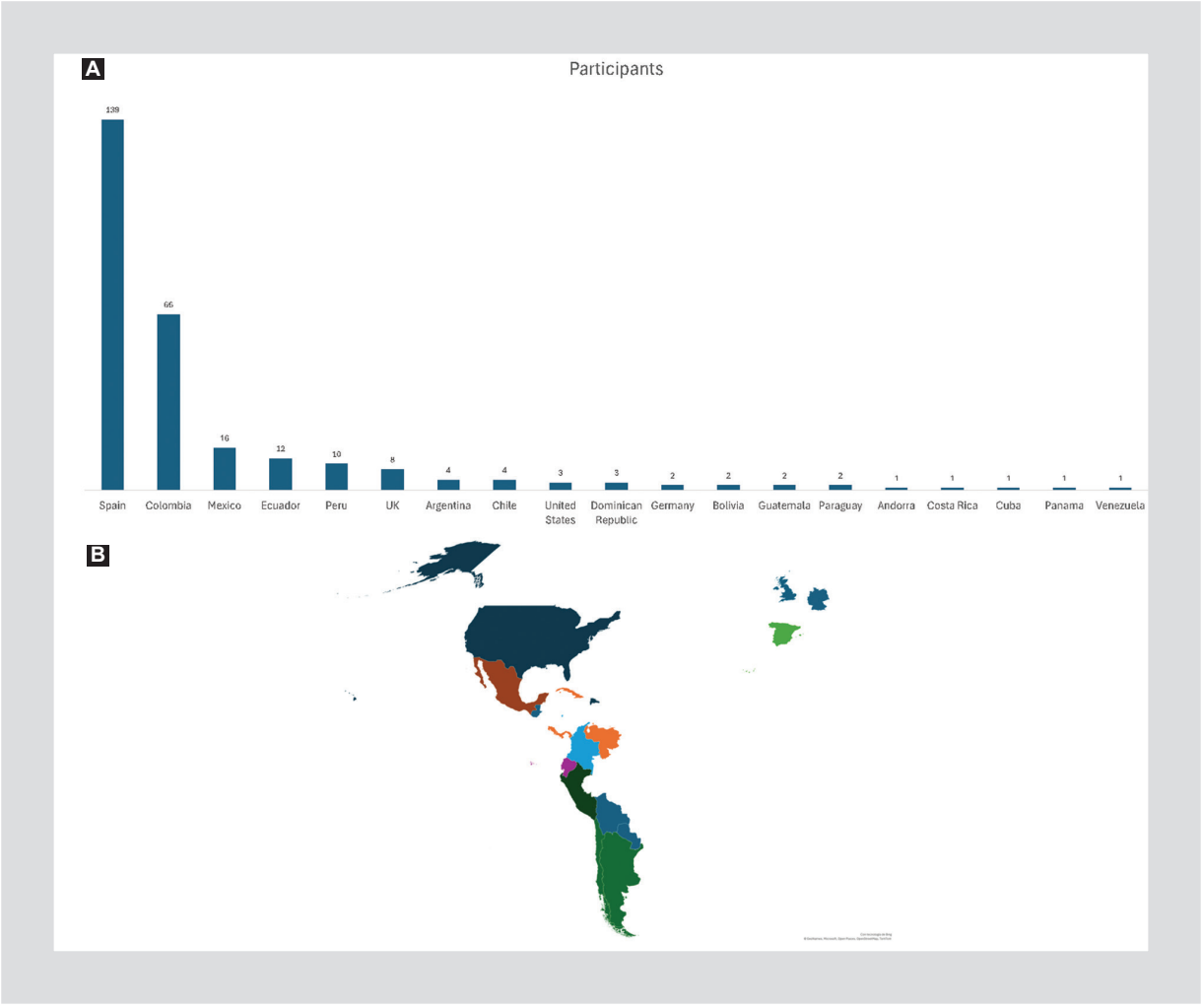

Figure 1. *Distribution of attendees at the 1st Spanish Conference on Genomic Medicine.* **A:** *number of participants per country.* **B:** *countries represented.*

conflicting or incomplete. Adherence to these guidelines, however, helps standardize the interpretation process across different laboratories and clinicians. Computational tools and algorithms, such as PolyPhen[34], SIFT[35], and MutationTaster[36], are also used to predict the impact of variants on protein function. These tools, while valuable, have limitations in accuracy and often produce discordant results.

Interpreting genetic variants also requires considering the clinical context, including patient phenotype, family history, and other clinical findings. Collaborative efforts and data sharing among laboratories, clinicians, and researchers are critical for advancing variant interpretation. Initiatives such as the Global Alliance for Genomics and Health[37] and the Matchmaker Exchange[38] facilitate the sharing of variant data and phenotypic information, promoting a more comprehensive understanding of genetic variants and their clinical significance.

Significant challenges remain in variant interpretation, nevertheless. These include the need for more extensive and diverse population databases to reduce biases. Future directions in this field may involve the development of more sophisticated AI models, greater international collaboration, and continued efforts to refine and expand variant databases.

The case of genomics England

Genomics England represents a landmark effort in the integration of genomic data into clinical practice. Established in 2013 by the UK Department of Health,

Genomics England was tasked with delivering the 100,000 Genomes Project. One of the critical aspects of this initiative was its focus on rare diseases and cancer.

Rare diseases, by definition, are often difficult to diagnose due to the limited availability of clinical information and low rate. By sequencing the genomes of patients with rare diseases and their families, the project aimed to uncover the genetic underpinnings of these conditions, leading to more accurate diagnoses and better-targeted treatments.

Genomics England also analyzed both tumor and normal tissues from the same patient affected by cancer, providing insights into the genetic changes driving and paving the way for personalized treatment strategies. The project has also focused on the development of standardized protocols for data sharing and patient consent, addressing critical issues related to data privacy and ethical considerations in genomic research.

The integration of genomic data into the UK's NHS has been a key focus of Genomics England. The project has worked closely with NHS clinicians and policymakers to ensure that the genomic information generated can be effectively used in routine clinical care. This includes training health-care professionals in genomic medicine, developing clinical guidelines for the use of genomic data, and establishing pathways for the incorporation of genomic testing into the NHS diagnostic and treatment protocols. As a result, the project has laid the groundwork for the widespread adoption of genomic medicine within the NHS, setting a precedent for other national health-care systems.

Genomics England has also played a pivotal role in fostering public engagement and awareness about genomic medicine. The project has undertaken extensive outreach efforts to educate the public about the benefits and implications of genomic research, promoting transparency and building trust in the use of genomic data in health care. This has been crucial in encouraging patient participation and ensuring the long-term success of the project. By demonstrating the potential of genomic medicine to transform health care, Genomics England has set a benchmark for future initiatives in this rapidly evolving field.

Genomics in Latin America

The genomic landscape in Latin America is rapidly evolving, driven by the region's unique human genetic diversity and the increasing recognition of the importance of personalized medicine. Latin America is characterized by a rich mosaic of ancestries, including Indigenous Amerindians, European, African, and Asian populations. This diverse genetic heritage offers a valuable resource for understanding the genetic basis of diseases and developing targeted therapies. However, the region faces significant challenges in fully realizing the potential of genomic medicine, including limited infrastructure, funding constraints, and the need for greater integration of genomic data into health-care systems.

One of the primary strengths of genomics in Latin America is its potential to uncover genetic variants that are specific to the region's populations. These variants may contribute to the prevalence and manifestation of certain diseases, offering insights that are not accessible through studies conducted in predominantly European or North American populations. For example, research in Latin America has identified unique genetic factors associated with diseases such as Chagas disease[39], type 2 diabetes[40], and various forms of cancer[41,42]. These findings are crucial for developing region-specific diagnostic tools and treatments.

Despite these strengths, the implementation of genomic medicine in Latin America faces several barriers. Infrastructure for genomic research and clinical applications is often underdeveloped compared to other countries. Many laboratories lack the advanced sequencing technologies and computational tools necessary for large-scale genomic studies. Furthermore, there is a shortage of trained bioinformaticians and geneticists, which hampers the ability to analyze and interpret genomic data effectively.

Funding is another significant challenge. While there are pockets of excellence and some well-funded research initiatives, overall investment in genomic research in Latin America is limited. This financial constraint affects the ability to conduct large-scale studies and implement genomic medicine broadly across the region. International collaborations and partnerships are crucial in bridging these gaps, providing access to funding, expertise, and advanced technologies.

Ethical and regulatory considerations also play a critical role in the development of genomics in Latin America. Ensuring that genomic research respects the rights and privacy of participants, particularly Indigenous communities, is paramount[43]. These populations have historically been underrepresented in genetic research, and there is a need for frameworks that promote ethical engagement and equitable benefits from genomic discoveries[44]. Efforts to address these con-

cerns are underway, with several countries in the region developing guidelines and policies to govern genomic research.

Several national initiatives are helping to advance the field of genomics in Latin America. For instance, the Brazilian Initiative on Precision Medicine aims at integrating genomic data into clinical practice[45] through a national database of genomic information. Its main goal is facilitating research and the development of personalized therapies. Similarly, Mexico's National Institute of Genomic Medicine has been established for genomic research and its application to public health[46]. Thus, by leveraging its genetic diversity, the region can contribute valuable insights to the global understanding of genetic diseases and the development of personalized therapies, ultimately improving health-care outcomes for its populations.

Genomics in Spain

The genomics landscape in Spain is marked by significant advancements and challenges. Despite the progress in genomic research and the establishment of advanced infrastructure, the lack of recognition of genetics as an independent medical specialty in Spain poses substantial hurdles to the effective delivery of genomic care.

Infrastructure for Personalized Medicine associated with Science and Technology (IMPaCT) is a pioneering initiative in Spain aimed at advancing precision medicine by creating a robust infrastructure that integrates genomic, clinical, and data science. It is part of Spain's broader strategy to harness the potential of personalized medicine to improve health-care outcomes. IMPaCT focuses on developing comprehensive cohorts, enhancing genomic capabilities, and leveraging data science to enable precise and individualized treatments. This initiative also seeks to align with European efforts, such as the European Genomic Data Infrastructure and the 1+ Million Genomes project, to promote synergies and standardize practices across borders. Through these efforts, IMPaCT is poised to significantly enhance the landscape of precision medicine in Spain, contributing to better health outcomes and setting a benchmark for other countries to follow.

Despite these advancements, the fact that genetics is not recognized as an official medical specialty in Spain significantly impairs the delivery of genomic care. This lack of formal recognition means that there is no structured pathway for training and certifying medical geneticists. Consequently, health-care professionals with specialized training in genetics often lack the formal qualifications needed to practice as medical specialists, limiting their ability to integrate genomic insights into patient care effectively.

The lack of formal recognition for genetics as a specialty impacts the integration of genomic medicine into routine clinical practice. Without a recognized specialty, there is limited awareness and understanding of genomic medicine among other health-care professionals. This gap in knowledge can lead to underuse of genomic tests and missed opportunities for personalized treatment approaches. For instance, oncologists and other specialists may not be fully equipped to incorporate genomic data into their treatment plans, potentially limiting the effectiveness of precision medicine.

In countries where genetics is an established medical specialty, professional societies and regulatory scientific/academic bodies develop standardized guidelines to ensure consistent and high-quality care. In Spain, the absence of a recognized specialty means that such guidelines are less likely to be developed or adopted, leading to variability in the quality of genomic services across different health-care settings.

Efforts to address these challenges are ongoing. Advocacy groups and professional organizations are working to raise awareness about the importance of recognizing genetics as a medical specialty. They argue that formal recognition would not only improve the quality of genomic care but also attract more professionals to the field, enhancing the overall capacity of the health-care system to deliver personalized medicine.

In the meantime, Spain continues to build its genomic infrastructure and participate in international collaborations. Organizations such as the Instituto de Salud Carlos III play a pivotal role in supporting genomic research and fostering collaboration among Spanish and international researchers. These efforts ensure that advances in genomics translate into tangible benefits for patients.

Host genomics and infectious diseases

Immunity in humans plays a critical role defending the body from external microorganisms and internal cancer cells. In this way, genetic abnormalities may compromise immune responses and make individuals more susceptible to infections and cancers.

Infectious microorganisms may result in clinical manifestations once they surpass the immune barriers.

Genetic variability between individuals may influence infections through three mechanisms: susceptibility, drug effect, and disease severity (Fig. 2). Some allelic variants may increase or reduce the risk of infection. As example, individuals with *CCR5* def 32 homozygous at chromosome 3 are "resistant" to HIV infection[47], whereas infected heterozygous progresses slowly to advanced immunodeficiency and acquired immunodeficiency syndrome[48].

Pharmacogenomics is also important for proper HIV management. A paradigm was established when *HLA-B*5701* testing became mandatory before prescribing abacavir. The marker is present in over 5% of Caucasians and up to half of carriers may experience hypersensitivity reactions, including Stevens-Johnson syndrome/toxic epidermic necrolysis, following drug exposure[49].

The response to interferon α in chronic hepatitis C and more recently in chronic hepatitis B has been shown to be strongly influenced by genetics (Fig. 3). C alleles at the interferon lambda (*IL28b*) gene at chromosome 19 lead to greater therapeutic viral clearance in hepatitis C[50]. The same genetic trait also influences viral load and liver fibrosis progression[51,52]. Similarly, C alleles at the *TP53BP2* gene in chromosome 1 increase clearance of the hepatitis B surface antigen in chronic hepatitis B carriers[53].

The knowledge of genetic traits predisposing to certain infections may prone to closer follow-up and make earlier diagnosis (Table 1). On the other hand, the development of certain clinical conditions might raise clinical suspicion of underlying genetic conditions (Table 2). As example, mutants at *EVER1* or *EVER2* genes at chromosome 17 could account for disseminated wars in epidermodysplasia verruciformis[54]. This rare condition frequently affects individuals with parent consanguinity.

The recent COVID-19 pandemic has stimulated in an unprecedented way the potential contribution of host genomics to human clinical traits. Genetic determinants of both severe COVID[15] and long COVID[55] have been identified that may help identifying in advance the most vulnerable populations to severe acute respiratory syndrome coronavirus 2 infection and adopt preventive measures, such as prophylactic vaccines and early antiviral medications[56].

Ethical and implementation challenges

The implementation of genomic medicine in Spanish-speaking countries presents numerous ethical challenges that need to be addressed to ensure the responsible and equitable use of genomic technologies. These challenges span issues of privacy, informed consent, equity, representation, and societal impact, each requiring careful consideration and proactive measures.

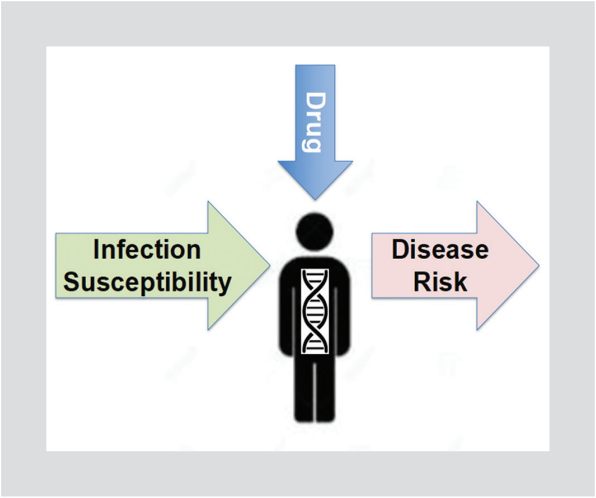

Figure 2. *Influence of genetics/genomics on infectious diseases.*

One of the foremost ethical challenges is the protection of patient privacy. Genomic data contain highly sensitive information that can reveal much about an individual's health, predisposition to diseases, and even ancestry. The potential for misuse of this data is a significant concern. Spanish-speaking countries must develop and enforce robust legal frameworks to safeguard genomic data. While the general data protection regulation in Europe provides a comprehensive model for data protection, Latin American countries must tailor their regulations to local contexts. This includes ensuring that genomic data are stored securely, access is restricted to authorized personnel, and data sharing is conducted under strict ethical guidelines.

Obtaining informed consent is a critical ethical requirement in genomic research and clinical practice. Participants must fully understand the implications of genomic testing, including potential risks, benefits, and the nature of the data being collected. In some Spanish-speaking countries, achieving truly informed consent can be challenging due to varying levels of education and health literacy. Consent forms and procedures must be culturally sensitive and accessible, ensuring that all individuals, regardless of their background, can make informed decisions. This may involve

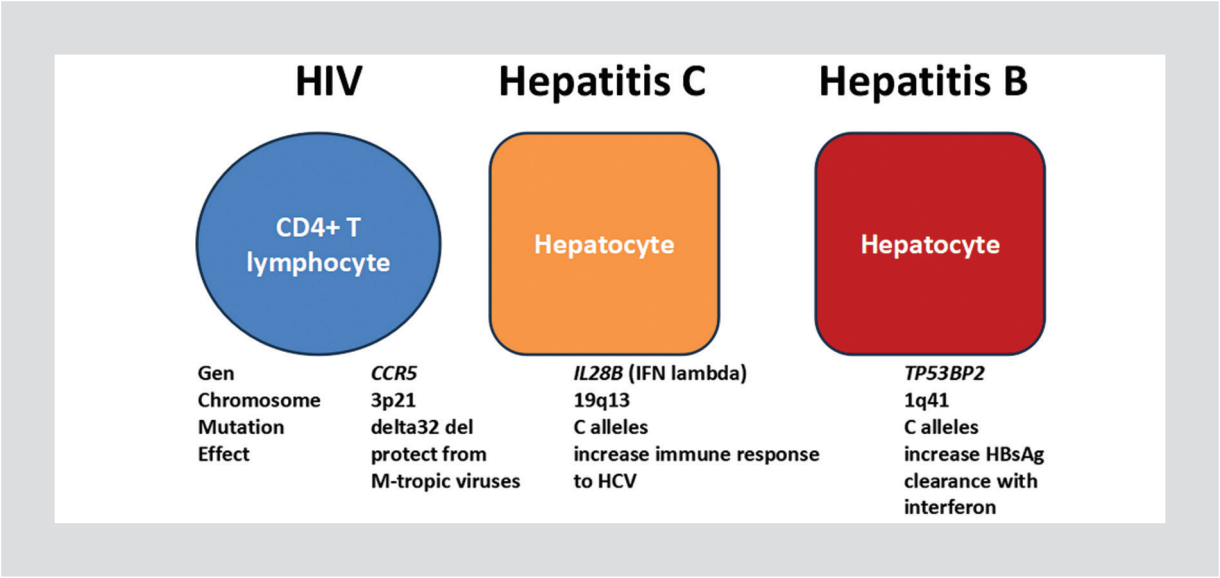

Figure 3. *Genetic determinants of viral control.*

Table 1. Genetic susceptibility to infections

Human gene	Infection	References
CCR5	HIV	21,22
IL28B	Hepatitis C	24-27
CISH (IL-2 signal pathway)	Tuberculosis, Malaria	29
Complement system	Meningococcus	30
PARK2	Lepra	31
FER	Pneumococcus sepsis	32

translating materials into local languages and dialects and employing community engagement strategies to explain complex genomic concepts in a comprehensible manner.

Equity in access to genomic medicine is a significant ethical issue. The high cost of genomic testing and therapies can create disparities in health-care access, with wealthier individuals benefiting disproportionately. Spanish-speaking countries, many of which have significant economic inequalities, must address these disparities to prevent the exacerbation of existing health inequities. This involves investing in public health-care infrastructure, subsidizing the cost of genomic tests and treatments, and ensuring that these services are available to underserved and marginalized communities. Policymakers need to create strategies that democratize access to genomic medicine, ensuring that its benefits are equitably distributed across all segments of society.

Historically, genomic research has predominantly involved populations of European descent, leading to a bias in genetic databases and research outcomes[57]. Spanish-speaking countries, with their diverse genetic backgrounds, could contribute significantly to a more inclusive global genomic dataset. However, ensuring that underrepresented populations, including Indigenous and Afro-descendant communities, are adequately represented in genomic research presents an ethical challenge. Researchers must engage with these communities respectfully and ethically, ensuring that they benefit from the research and are not exploited. This includes obtaining proper consent, providing clear information about the research aims and outcomes, and sharing benefits equitably.

The potential for genetic information to be used discriminatorily in employment, insurance, and other areas of life is a critical ethical concern. In Spanish-speaking countries, it is essential to establish legal protections that prevent genetic discrimination. These protections should ensure that individuals are not unfairly treated based on their genetic information. For example, genetic data should not be used to deny

Table 2. Clinical suspicion for underlying genetic variants

Disease	Microorganism	Gene	Heritability
Skin and mucosae			
Disseminated wars	Papillomavirus	*EVER1* (*TMC6*) y *EVER2* (*TMC8*)	Recessive
Lung papillomatosis	Papillomavirus	*NLRP1*	Recessive
Kaposi's sarcoma	HHV-8	*OX40*	Recessive
Lepra	Mycobacterium leprae	*PARK2*	Recessive
Neurological			
Frontal encephalitis	HSV-1	*UNC93B1, IFNAR1, TLR3, TICAM1*	Recessive
	VZV	*POL3RA, POL3RC*	Dominant
Cerebral trunk encephalitis	Echovirus-30	*TLR3*	Recessive
	Enterovirus-71	*MDA5*	Recessive
Mollaret's meningitis	HSV-2	*ATGA4, LC3B2*	Dominant
Bacterial meningitis	Meningococcus	C5-C9 complement deficiencies	Recessive
Pulmonary			
Bilateral pneumonía	Influenza	*IRF7, IRF9*	Recessive
	Aviar influenza	*MX1*	Recessive
	COVID-19	*IFNAR1, IRF7*	Recessive
Pulmonary focal infection	Tuberculosis	*CISH* (IL-2 signaling)	Recessive
Systemic			
Fulminant hepatitis	Hepatitis A virus	*IL18BP*	Recessive
Disseminated infection	CMV	*NO52*	Recessive
	Pneumococcus	*FER*	Recessive
Resistance to infection	HIV-1	*CCR5*	Recessive
	Norovirus	*FUT2*	Recessive
Susceptibility to chronicity	Hepatitis C virus	*IL28B*	Recessive

insurance coverage or employment opportunities. Establishing clear policies and regulations to prevent genetic discrimination is essential to maintaining public trust in genomic medicine and encouraging people to participate in genomic research and testing[58].

Public trust in genomic medicine is essential for its successful implementation. Spanish-speaking countries must invest in education and public engagement to demystify genomics and highlight its potential benefits and ethical complexities. This includes integrating genomics into medical and health education curricula, conducting public awareness campaigns, and fostering an open dialogue about the ethical challenges and societal implications of genomics. By educating the public and involving them in decision-making processes, these countries can build a foundation of trust and support for genomic initiatives.

Accelerating access to global medical genomics

In the report of the World Health Organization (WHO) Scientific Council titled "Accelerating Access to Genomics for Global Health"[59], four strategies are discussed: promotion, application, collaboration, and ethical, legal, and social issues. In line with this document and its objectives, the first Spanish Congress on Genomic Medicine facilitated the promotion of the current and future uses of genomic medicine as well as the work that has impacted its use in medical genetics not only in European countries but also in Latin America. In addition, the event addressed possible strategies for the application of these technologies in developing countries and the collaboration between professionals from different countries. The discussion spaces within the event allowed for the free exchange of ideas regarding the ethical, legal, and social issues of the use and application of genomic medicine not only in Spain but also globally. With all this, we believe that the first Spanish Congress on Genomic Medicine was in aligned with the WHO recommendations in its goal of accelerating access to genomic medicine for global health, and we hope that in future editions, we will continue to contribute to this objective.

Conclusion

The advancement of genomic medicine holds immense potential for transforming health care in Spanish-speak-

ing countries by enabling personalized treatment, improving disease prevention, and fostering new scientific discoveries. However, the successful implementation of genomic technologies faces numerous challenges that must be addressed through concerted efforts in infrastructure development, ethical considerations, and public engagement.

Despite significant progress in genomic research and the establishment of advanced infrastructure in many Spanish-speaking countries, several critical issues remain. The lack of recognition of genetics as an independent medical specialty in countries such as Spain impacts the delivery of genomic care, highlighting the need for formalized training pathways and professional certification to develop a robust workforce capable of integrating genomics into clinical practice.

Ethical challenges are particularly notable in the context of genomics. Protecting patient privacy, ensuring informed consent, promoting equity and access, and preventing genetic discrimination are paramount to maintaining public trust and ensuring the ethical use of genomic data. Spanish-speaking countries must adopt comprehensive legal frameworks and culturally sensitive practices to address these issues effectively. Moreover, equitable representation in genomic research is essential to ensure that the benefits of genomic medicine are accessible to all populations, including those historically underrepresented in scientific studies.

Public education and engagement are crucial components for the future of genomics. By raising awareness about the benefits and ethical complexities of genomic medicine, Spanish-speaking countries can foster a supportive environment for genomic initiatives. Educational programs and public discourse can help demystify genomics, promote informed decision-making, and build public trust in genomic technologies.

While the journey to fully integrate genomics into health-care systems in Spanish-speaking countries is fraught with challenges, the potential benefits are substantial. By addressing ethical concerns, enhancing infrastructure, and fostering international and regional collaborations, these countries can unlock the transformative power of genomics. This will not only improve health outcomes and advance scientific knowledge but also ensure that the promise of personalized medicine is realized in an inclusive and equitable manner.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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