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Multisociety Mexican Consensus on the integration of polygenic risk in cardiovascular risk stratification: implications for precision cardiovascular medicine in Mexico+

Consenso multisocietario mexicano sobre la integración del riesgo poligénico en la estratificación del riesgo cardiovascular: implicaciones para la medicina cardiovascular de precisión en México

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Palabras clave:
Puntuación de riesgo poligénico, calcio en las arterias coronarias, registro mexicano de riesgo poligénico.

ABSTRACT

Introduction: cardiovascular disease remains the leading cause of mortality in Mexico, accounting for approximately one in four deaths nationwide. The epidemiological transition is characterized by a high prevalence of obesity, type 2 diabetes mellitus, hypertension, and atherogenic dyslipidemia from early stages of life, resulting in prolonged cumulative cardiometabolic exposure and earlier onset of atherosclerotic events. Traditional risk models, based on phenotypic variables and strongly dependent on chronological age, tend to underestimate biological susceptibility in younger individuals. **Objective:** to establish a multisociety position on the clinical use of Polygenic Risk Scores (PRS) in Mexico and to define a national implementation strategy linked to real-world evidence generation through the PRS-MX Registry. **Material and methods:** this consensus document was developed through a structured literature review and a modified Delphi methodology involving national experts in clinical cardiology, interventional cardiology, lipidology, genetics, and public health. **Results:** PRS is independent of traditional risk factors, improves risk reclassification in primary prevention, and identifies individuals with greater absolute benefit

RESUMEN

Introducción: *las enfermedades cardiovasculares siguen siendo la principal causa de mortalidad en México, ya que representan aproximadamente una de cada cuatro muertes en todo el país. La transición epidemiológica se caracteriza por una elevada prevalencia de obesidad, diabetes mellitus tipo 2, hipertensión y dislipidemia aterogénica desde las primeras etapas de la vida, lo que da lugar a una exposición cardiometabólica acumulada prolongada y a una aparición más temprana de eventos ateroscleróticos. Los modelos de riesgo tradicionales, basados en variables fenotípicas y fuertemente dependientes de la edad cronológica, tienden a subestimar la susceptibilidad biológica en individuos más jóvenes.* ***Objetivo:*** *establecer una postura conjunta de varias sociedades sobre el uso clínico de las puntuaciones de riesgo poligénico (PRS) en México y definir una estrategia nacional de implementación vinculada a la generación de evidencia del mundo real a través del Registro PRS-MX.* ***Material y métodos:*** *este documento de consenso se elaboró mediante una revisión de la literatura estructurada y una metodología Delphi modificada, en la que participaron expertos nacionales en cardiología clínica, cardiología intervencionista,*

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from lipid-lowering therapies. A three-dimensional model integrating phenotype, anatomy, and genotype is proposed. **Conclusions:** selective implementation of PRS in Mexico represents a step toward precision cardiovascular medicine and should be carried out in a stepwise manner linked to national evidence generation.

*lipidología, genética y salud pública. **Resultados:** el PRS es independiente de los factores de riesgo tradicionales, mejora la reclasificación del riesgo en la prevención primaria e identifica a las personas que obtienen un mayor beneficio absoluto de los tratamientos hipolipemiantes. Se propone un modelo tridimensional que integra el fenotipo, la anatomía y el genotipo. **Conclusiones:** la implementación selectiva de la PRS en México supone un paso hacia la medicina cardiovascular de precisión y debería llevarse a cabo de forma gradual, ligada a la generación de evidencia a nivel nacional.*

Abbreviations:
PRS = Polygenic Risk Score
CAC = Coronary Artery Calcium
LDL-C = Low-Density Lipoprotein Cholesterol
Lp(a) = Lipoprotein(a)
PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9
ESC = European Society of Cardiology
PRS-MX = Mexican Polygenic Risk Registry

KEY MESSAGES

What is new?

1. This is the first multisociety consensus addressing the clinical integration of polygenic risk in cardiovascular prevention in Mexico.
2. Polygenic Risk Scores (PRS) redefine cardiovascular risk as a lifelong trajectory, rather than a short-term probability.
3. A novel three-dimensional model integrating phenotype, anatomy (Coronary Artery Calcium CAC), and genotype (PRS) is proposed as a framework for precision cardiovascular risk stratification.

What are the clinical implications?

1. PRS enables early identification of individuals with accelerated atherosclerotic trajectories, particularly in young adults and those at intermediate risk.
2. The integration of PRS with CAC and traditional risk factors improves clinical decision-making in primary prevention.
3. Implementation should be selective and evidence-based, linked to national validation through the PRS-MX Registry.
4. Precision cardiovascular prevention strategies may optimize resource allocation by targeting individuals with the greatest expected benefit.

INTRODUCTION

Cardiovascular disease remains the leading cause of mortality in Mexico, accounting for approximately one quarter of all registered deaths nationwide.[1] This occurs in the context of an epidemiological transition characterized by a high prevalence of obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease, and atherogenic dyslipidemia beginning early in life.[2-5] The pathophysiological consequence is prolonged cumulative exposure to apolipoprotein B-containing lipoproteins, low-grade systemic inflammation, and endothelial dysfunction, leading to the development of subclinical atherosclerosis decades before clinical manifestation.

Contemporary risk prediction models have substantially improved cardiovascular prevention by integrating variables such as age, sex, blood pressure, lipid profile, smoking status, and diabetes into validated multivariable equations.[6,7] However, these models are predominantly phenotypic and rely heavily on chronological age as a determinant of risk. In populations with early cardiometabolic exposure, such as the Mexican population, this temporal dependence results in systematic underestimation of true biological susceptibility.

Evidence from Mendelian randomization studies has demonstrated that cumulative lifetime exposure to Low-Density Lipoprotein Cholesterol (LDL-C) is a central determinant of atherosclerotic cardiovascular disease risk, and that modest but sustained reductions from early life are associated with substantially greater reductions in cardiovascular risk than intensive reductions initiated later.[8-11] This paradigm underscores the need for tools capable of identifying risk trajectories from birth.

Polygenic Risk Scores (PRS) quantify this biological susceptibility through the weighted integration of multiple common genetic variants associated with coronary artery disease.[12-15] Their incorporation into clinical practice represents a transition toward precision cardiovascular medicine.

CONSENSUS METHODOLOGY

This document was developed by the Working Group on Cardiovascular Prevention and Precision Medicine of the Mexican Association for the Prevention of Atherosclerosis and its Complications (AMPAC for its abbreviation in spanish), in collaboration with the National Association of Cardiologists of Mexico (ANCAM for its abbreviation in spanish), the Mexican Society of Cardiology (SMC for its abbreviation in spanish), the National Association of Cardiologists of ISSSTE (ANCISSSTE for its abbreviation in spanish), and the National Association of Cardiologists of Centro Médico La Raza (ANCCMR for its abbreviation in Spanish).

A structured literature review was conducted using PubMed, EMBASE, and the Cochrane Library from January 2005 to December 2025. The review included genome-wide association studies, meta-analyses of polygenic risk scores, clinical validation studies, risk reclassification analyses, and subanalyses of lipid-lowering clinical trials.

Evidence appraisal incorporated discrimination, calibration, net reclassification improvement, integrated discrimination improvement, and absolute risk reduction.

Relevant international guidelines, particularly those from the European Society of Cardiology and North American cardiovascular societies, were reviewed.[6,7,16-18] Recommendations were developed through expert consensus and categorized according to classes of recommendation and levels of evidence based on the European Society of Cardiology framework.

The final content was reviewed and approved by all members of the AMPAC–ANCAM–SMC–ANCISSSTE–ANCCMR consensus group, ensuring applicability within the Mexican healthcare system.

THREE-DIMENSIONAL MODEL OF CARDIOVASCULAR RISK STRATIFICATION

The integration of PRS into clinical practice *(Figure 1)* should not be interpreted as a replacement of existing risk assessment tools, but rather as the incorporation of a third dimension into cardiovascular risk stratification.

Traditionally, risk estimation has relied on phenotypic variables that reflect the patient's current clinical status and allow estimation of short- and intermediate-term event probability.

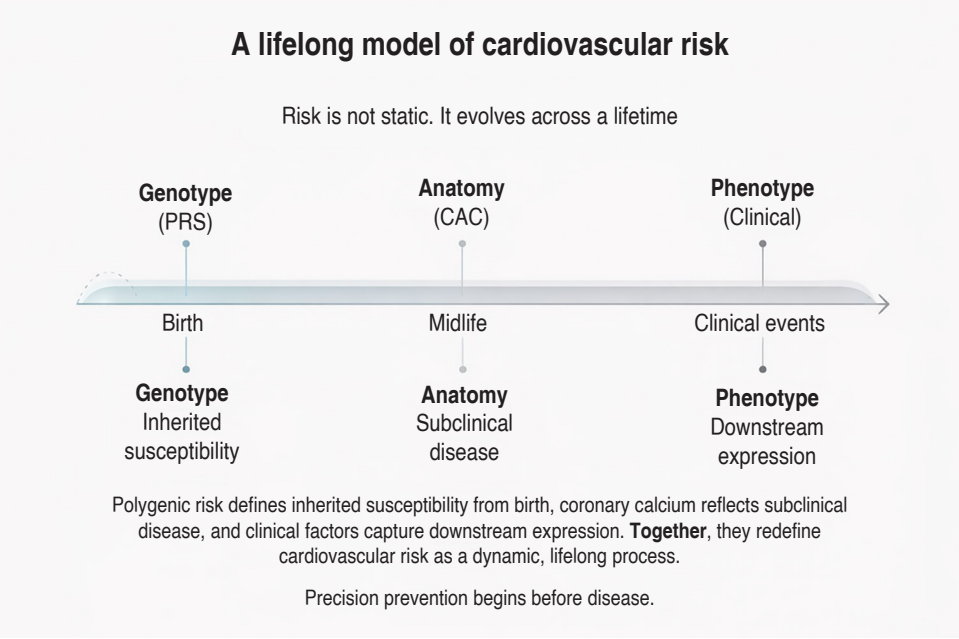

Figure 1:

Three-dimensional model of cardiovascular risk stratification: phenotype, anatomy, and genotype. A conceptual framework integrating phenotypic risk factors, anatomical burden of subclinical atherosclerosis assessed by coronary artery calcium, and genetic susceptibility captured by polygenic risk scores (PRS). Together, these dimensions redefine cardiovascular risk as a **dynamic, lifelong trajectory**, enabling a more precise and individualized approach to risk stratification. CAC = Coronary Artery Calcium. PRS = Polygenic Risk Scores.

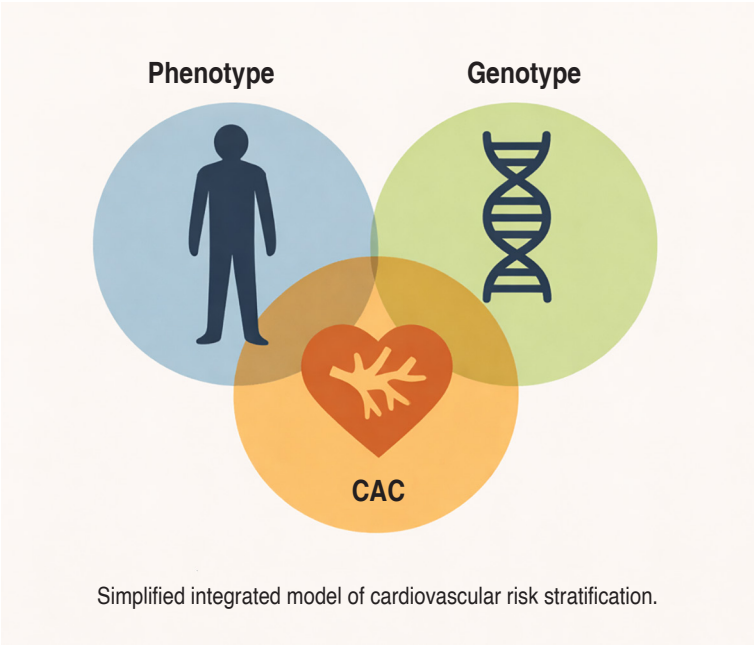

Figure 2: Simplified integrated model of cardiovascular risk stratification. CAC = Coronary Artery Calcium.

The introduction of Coronary Artery Calcium (CAC) scoring added an anatomical dimension, enabling the detection of established subclinical atherosclerosis. PRS introduces a genotypic dimension that captures inherited susceptibility and enables estimation of the biological risk trajectory from birth.

Together, these three domains (phenotype, anatomy, and genotype) form a unified, multidimensional framework for cardiovascular risk assessment,[6,12,19] as illustrated in *Figure 2*.

This model addresses three fundamental clinical questions: what is the patient's current risk, whether subclinical atherosclerotic disease is already present, and what is the expected trajectory of disease progression over time.

From a temporal perspective, PRS operates upstream, CAC reflects an intermediate stage of disease, and phenotypic models capture downstream clinical expression. This sequential framework explains why PRS has its greatest clinical impact early in life, whereas CAC becomes more informative in midlife.

The integration of these dimensions enables a dynamic and individualized approach to risk stratification and represents a conceptual foundation for precision cardiovascular medicine.

Schematic representation of the interaction between phenotype, genotype, and coronary artery calcium (CAC) as complementary components of cardiovascular risk assessment. The overlap illustrates the integrated nature of

biological susceptibility, subclinical disease, and clinical expression within a unified precision medicine framework. This model addresses three fundamental clinical questions: what is the patient's current risk, whether subclinical atherosclerotic disease is already present, and what is the expected trajectory of disease progression over time.

From a temporal perspective, PRS operates upstream, CAC reflects an intermediate stage of disease, and phenotypic models capture downstream clinical expression. This sequential framework explains why PRS has its greatest clinical impact early in life, whereas CAC becomes more informative in midlife.

The integration of these dimensions enables a dynamic and individualized approach to risk stratification and represents a conceptual foundation for precision cardiovascular medicine.

PRS, CORONARY ARTERY CALCIUM, AND LIPOPROTEIN(A): COMPLEMENTARY TOOLS

Coronary artery calcium scoring has consistently demonstrated its ability to refine cardiovascular risk stratification in primary prevention, particularly among individuals classified as having intermediate risk.[19,20] A CAC score of zero is associated with very low short-term risk, whereas higher values identify individuals with substantially increased risk.

However, CAC reflects established disease rather than underlying biological susceptibility. In younger individuals with high genetic risk, the absence of calcification does not exclude an active atherosclerotic process.

Table 1: Integrated framework combining polygenic risk score, coronary artery calcium, and lipoprotein(a) for cardiovascular risk stratification.

Tool	What it captures	Biological timing
PRS	Genetic susceptibility	Lifelong (from birth)
CAC	Subclinical atherosclerosis	Intermediate stage
Lp(a)	Inherited thrombogenic risk	Constant

CAC = Coronary Artery Calcium. Lp(a) = lipoprotein(a). PRS = Polygenic Risk Score.

In this context, PRS provides a measure of inherited susceptibility and enables identification of accelerated risk trajectories decades before the development of detectable calcification.

Lipoprotein(a) [Lp(a)] is a genetically determined, causal, and independent risk factor for atherosclerotic cardiovascular disease, as supported by genetic and epidemiological evidence.[21] Unlike PRS, which integrates multiple biological pathways, Lp(a) reflects a specific proatherogenic and prothrombotic mechanism.

The combined assessment of PRS, CAC, and Lp(a) allows a comprehensive characterization of cardiovascular risk by integrating biological susceptibility, disease burden, and thrombogenic potential *(Table 1)*.

HIGH-IMPACT CLINICAL SCENARIOS IN MEXICO

The clinical value of PRS is greatest in scenarios where discordance exists between estimated risk based on traditional models and clinical judgment *(Table 2)*.

In young adults with a family history of premature coronary artery disease, chronological age significantly lowers calculated risk in conventional algorithms. This often leads to delayed implementation of preventive strategies despite the presence of adverse metabolic profiles. PRS enables the identification of individuals with accelerated atherosclerotic trajectories who may benefit from earlier intervention.[10,13,22]

Individuals classified as having intermediate risk represent the primary zone of therapeutic uncertainty in primary prevention. The incorporation of PRS allows reclassification toward higher or lower biological risk, optimizing clinical decision-making and resource allocation.[11,15,23,24]

In women undergoing menopausal transition, PRS may help differentiate between metabolic changes related to aging and underlying biological susceptibility, facilitating more individualized prevention strategies.

In early cardiorenal–metabolic syndrome (characterized by central obesity, hypertriglyceridemia, reduced HDL-C, and insulin resistance) PRS enables identification of high-risk phenotypes with accelerated disease progression.

Table 2: Clinical scenarios in which polygenic risk score may modify decision-making in primary prevention.

Recommendation	Class	Level
Use of PRS in young adults with family history of premature coronary artery disease	IIa	B
Use of PRS in individuals with intermediate risk and therapeutic uncertainty	IIa	B
Use of PRS to support intensification of lipid-lowering strategies in primary prevention	IIb	B
PRS should not be used as a standalone decision-making tool	III	C
Validation of PRS in the Mexican population prior to widespread implementation	I	C

PRS = Polygenic Risk Score.
Classification of recommendations and levels of evidence adapted from the European Society of Cardiology (ESC) Guidelines.[6,7,16]

Table 3: Classes of recommendation and levels of evidence.

Class	Definition
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the treatment or procedure is not useful/effective and in some cases may be harmful
Level	**Source of evidence**
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of expert opinion and/or small studies, retrospective studies, registries

Classification of recommendations and levels of evidence adapted from the European Society of Cardiology (ESC) Guidelines.[6,7,16]

CONSENSUS RECOMMENDATIONS

Recommendations are categorized according to classes of recommendation and levels of evidence, as defined in *Table 3*.

THERAPEUTIC IMPLICATIONS AND ABSOLUTE RISK REDUCTION

Contemporary guidelines recommend tailoring lipid-lowering therapy according to global cardiovascular risk.[21,25] In this context, PRS introduces an additional dimension by identifying individuals who are more biologically susceptible and, consequently, who have a greater potential for absolute benefit from intervention.

Evidence derived from clinical trial subanalyses has demonstrated that individuals with higher polygenic risk derive the greatest absolute reduction in cardiovascular events with statin therapy, despite achieving similar reductions in LDL-C levels.[11] This finding supports a precision medicine approach in

which treatment intensity is aligned with underlying biological risk rather than solely phenotypic profiles.

Similarly, in the FOURIER and ODYSSEY OUTCOMES trials, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors provided the greatest benefit to individuals with higher baseline risk. Notably, risk reduction did not reach statistical significance in individuals with low or intermediate polygenic risk, reinforcing the concept of allocating high-cost therapies to those with the highest expected benefit.[26,27]

From a clinical perspective, PRS should be interpreted as a modifier of risk that refines therapeutic decision-making, rather than as an isolated determinant.

IMPACT ON INTERVENTIONAL CARDIOLOGY

Interventional cardiology in Mexico faces a high burden of complex atherosclerotic disease in relatively young patients. Early identification of individuals with accelerated risk trajectories has the potential to reduce the incidence of premature multivessel disease, decrease the need for complex revascularization procedures, and modify the epidemiological profile of coronary artery disease.

From this perspective, PRS is not only a primary prevention tool but also a strategy with long-term implications for interventional cardiology practice.

HEALTH ECONOMICS AND RESOURCE ALLOCATION

The incorporation of genomic tools into healthcare systems with constrained resources requires evaluation not only of diagnostic performance but also of cost-effectiveness and resource allocation.

In middle-income countries, preventive strategies that target individuals at the highest absolute risk have been the most effective at reducing cardiovascular events.[28,29] By identifying individuals with accelerated risk trajectories early in life, PRS enables more targeted and intensive interventions in selected populations.

This approach is particularly relevant in Mexico, where premature cardiovascular disease imposes a substantial burden in terms of disability-adjusted life years and indirect costs related to loss of productivity.

From this perspective, PRS should be considered not merely as a diagnostic tool, but as a stratification instrument capable of optimizing the allocation of high-cost therapies—such as PCSK9 inhibitors, ezetimibe, or combination lipid-lowering strategies—to individuals with the greatest expected clinical benefit.[26-29]

MEXICAN POLYGENIC RISK REGISTRY (PRS-MX)

The clinical implementation of PRS in Mexico must be closely linked to the generation of national evidence through the PRS-MX Registry, designed as a prospective, multicenter, real-world cohort.

The initial enrollment phase will extend through the third quarter of 2026, with potential extension depending on recruitment dynamics. The primary objective is to evaluate the impact of PRS on therapeutic decision-making in primary prevention.

Secondary objectives include assessment of LDL-C target achievement, intensification of lipid-lowering therapy, treatment adherence, and incidence of cardiovascular events during follow-up.

The registry will systematically collect demographic variables, traditional risk factors, biochemical parameters, treatment strategies, therapeutic targets, and clinical outcomes. This design will enable evaluation of the real-world effectiveness of PRS and support calibration of predictive models in the Mexican population.

Its collaborative structure will allow broad national participation and ensure recognition of contributing investigators in subsequent publications.

CUMULATIVE EXPOSURE TO APOB-CONTAINING LIPOPROTEINS: A UNIFYING PARADIGM

The concept of cumulative exposure to atherogenic lipoproteins provides the pathophysiological link between genetic susceptibility and clinical expression of coronary artery disease.

Mendelian randomization studies have demonstrated that sustained reductions in LDL-C from early life are associated with substantially greater reductions in cardiovascular risk compared with intensive reductions initiated later.[8-11,30] This time-dependent effect reflects the cumulative nature of atherosclerosis.

Importantly, the relationship between LDL-C levels and cardiovascular risk is modulated by polygenic background, resulting in heterogeneous risk trajectories among individuals with similar lipid profiles.[31-33]

PRS enables estimation of the expected rate of cumulative atherogenic exposure and, therefore, the lifelong trajectory of cardiovascular risk.

In populations characterized by early cardiometabolic exposure, such as Mexico, this paradigm highlights the limitations of age-based intervention thresholds and supports earlier, biology-driven prevention strategies.

PERFORMANCE OF PRS IN MULTIETHNIC POPULATIONS

The Mexican population presents a complex genetic architecture derived from admixture of Amerindian, European, and African ancestries, with significant regional variation.[34]

This multiethnic background has direct implications for the transferability of PRS developed in predominantly European populations. Recent studies have demonstrated that PRS retain their ability to stratify risk in non-European populations when adjusted for ancestry and recalibrated using local data, although with a modest reduction in discriminatory performance.[35-37]

This limitation does not represent a barrier, but rather a strong rationale for the generation of national evidence.

The PRS-MX Registry will enable evaluation of PRS performance in the Mexican population, development of locally calibrated models, and exploration of the interaction between genetic susceptibility and cardiometabolic exposure.

COMMUNICATION OF GENETIC RISK AND BEHAVIORAL CHANGE

Effective communication of genetic risk is a critical component of PRS implementation. Available evidence demonstrates that structured communication of genetic risk, framed within a modifiable risk model, does not induce biological determinism or significant anxiety. On the contrary, it improves adherence to lipid-lowering therapy and promotes sustained lifestyle changes.[38-40]

Clinical communication should emphasize the concept of a modifiable risk trajectory and the benefits of early intervention.

IMPLEMENTATION SCIENCE AND HEALTH SYSTEM INTEGRATION

The adoption of diagnostic innovations depends not only on scientific evidence but also on structured implementation pathways. Implementation science has demonstrated that successful integration requires progressive phases including academic validation, process standardization, clinician education, and evaluation of clinical and economic impact.[41]

In Mexico, PRS implementation should follow a stepwise model:

Phase 1: Controlled academic implementation in specialized centers

Phase 2: National validation through the PRS-MX Registry

Phase 3: Selective integration into broader cardiometabolic care networks

This structured approach prevents indiscriminate adoption and ensures evidence-based implementation.

ETHICAL AND LEGAL CONSIDERATIONS

The clinical use of genetic information requires a robust ethical and legal framework.

Informed consent must include clear explanation of the probabilistic nature of PRS, its limitations, and its complementary role relative to traditional risk assessment tools.

Genetic data must be protected according to national regulations and international standards of confidentiality and data security. Mechanisms should also be established to prevent discrimination based on genetic information in employment or insurance contexts.

PRS should be used exclusively within clinical and research settings and not for non-medical population screening purposes.

EVIDENCE GAPS

Despite rapid advances in cardiovascular genomics, important gaps remain. The absence of randomized clinical trials specifically designed to evaluate PRS-guided therapeutic strategies represents the main limitation.

Most available evidence derives from observational studies and post hoc analyses. Additional research is required to define intervention thresholds based on genetic risk percentiles and to integrate PRS into existing treatment algorithms.

Further areas of interest include its role in secondary prevention, residual risk assessment, and integration with imaging modalities such as coronary artery calcium in cost-effectiveness models.

NATIONAL RESEARCH AGENDA (2026-2030)

This consensus establishes a national research agenda focused on:

1. Development of PRS calibrated for the Mexican population
2. Evaluation in early cardiorenal–metabolic syndrome
3. Impact on treatment intensification and LDL-C target achievement
4. Integration with imaging tools in cost-effectiveness models
5. Role in secondary prevention and residual risk

This agenda aims to position Mexico as a regional leader in precision cardiovascular medicine.

LATIN AMERICAN PROJECTION

The development of a multisociety consensus and a national prospective registry represents a strategic opportunity to lead the advancement of clinical cardiogenomics in Latin America.

The genetic diversity of the Mexican population provides a unique model for studying the interaction between genetic susceptibility and cardiometabolic exposure.[34]

The generation of evidence in this context will support the development of risk prediction models applicable across Latin American populations and foster regional collaboration networks.

CONCLUSIONS

This document represents the first multisociety consensus on precision cardiovascular medicine in Mexico, establishing a paradigm shift in cardiovascular prevention. The incorporation of Polygenic Risk Scores (PRS) moves risk assessment beyond conventional short-term estimation, enabling characterization of lifelong risk trajectories from birth and redefining the temporal framework of preventive cardiology.

In a population characterized by early cardiometabolic exposure and a high burden of premature cardiovascular events, identifying individuals with accelerated atherosclerotic progression has profound clinical, epidemiological, and economic implications. Within this context, PRS provides a novel opportunity to refine risk stratification and anticipate disease development, supporting earlier and more intensive preventive strategies.

The integration of genetic risk with traditional clinical models allows a more precise and individualized assessment of cardiovascular risk, particularly among individuals classified as having intermediate risk, where clinical uncertainty is greatest. However, current evidence supports its role as an adjunct rather than a replacement for established risk prediction tools.

Despite its promise, PRS implementation faces challenges, including lack of standardization, heterogeneity across populations, and underrepresentation of Latin American cohorts. These limitations highlight the need for cautious, evidence-driven, and context-specific adoption.

Accordingly, PRS should be implemented through a selective, stepwise approach linked to national evidence generation through the PRS-MX Registry. This strategy will enable real-world evaluation, model calibration, and optimization of healthcare resource allocation.

The collaboration among national societies positions Mexico as a regional leader in clinical cardiogenomics and establishes the foundation for locally validated risk models with broader applicability across Latin America.

Ultimately, the clinical value of PRS will depend on its validation in diverse populations, integration into clinical frameworks, and incorporation into scalable, cost-effective precision medicine strategies.

In this evolving landscape, polygenic risk is not merely a predictor of disease, it is a lens through which the future of cardiovascular prevention can be redefined.

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