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Proteogenomics-Guided Risk-Based Screening for Coronary Artery Disease: Implementation across Diverse Populations and Equity Considerations

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ABSTRACT

Coronary artery disease (CAD) remains the leading cause of global morbidity and mortality, necessitating more effective and equitable preventive strategies. Proteogenomics-guided risk-based screening integrates genomic variation, circulating protein biomarkers, and clinical and environmental data to enhance risk prediction beyond traditional factors. This approach enables identification of individuals at elevated lifetime risk and supports targeted preventive interventions, potentially improving population health outcomes while optimizing resource allocation. However, implementation across diverse populations raises important methodological, ethical, and health-system challenges, including limited cohort diversity, variability in assay performance, data integration complexities, privacy governance, workforce capacity, and affordability constraints. Ensuring equitable deployment requires inclusive cohort development, standardized and validated assays, transparent computational models, and implementation frameworks grounded in community engagement and social determinants of health. Continuous monitoring of analytical validity, clinical validity, clinical utility, and equity metrics is essential within a learning health-system model. Proteogenomics-guided CAD screening, therefore, holds promise as a transformative precision public health strategy, provided that implementation prioritizes fairness, accessibility, and context-specific policy development to avoid exacerbating existing health disparities.

Keywords: Coronary Artery Disease**,** Proteogenomics**,** Risk-Based Screening**,** Precision Public Health**,** and Health Equity.

INTRODUCTION

Proteogenomics-guided risk-based screening for coronary artery disease: implementation across diverse populations and equity considerations [1]. Emerging genetic and proteomic science enables risk-based screening of coronary artery disease using individual multi-omics data, leading to substantial population health gains if targeted equitably [1]. Proteogenomics links environmental exposures and cellular mechanisms to risk differences by integrating multi-omics information across life stages and biological systems [2]. The approach generates population-level risk models, identifying individuals at elevated lifetime risk who are most likely to benefit from preventive interventions. Risk screening is particularly valuable for coronary artery disease due to its highly prevalent multifactorial aetiology and far-reaching health and economic consequences. Protecting the most disadvantaged, those with the highest risk who also face the most barriers to prevention, is fundamental to health equity [3]. Proteogenomics highlights risk-predictive markers and mechanisms that differ in effect across populations and identifies population-specific candidate biomarkers. Such differences arise from common genetic variation, differential exposure to environmental and lifestyle determinants, and social context [4]. These insights, combined with evidence of differential performance across metabolic, environmental, and lifestyle factors, suggest that the approach may be more effective and clinically actionable in some populations than others [5].

Conceptual Foundations of Proteogenomics in Coronary Artery Disease

Coronary artery disease (CAD) involves a progressive atherosclerotic plaque build-up in coronary arteries and is the leading cause of morbidity and mortality worldwide [2]. In Canada alone, CAD claims one life every 17

minutes. It is estimated that 6.5 million Canadians have been diagnosed with heart disease, and each year there are over 192,000 incidents of heart attack. CAD risk factors include dyslipidemia, hypertension, and diabetes; nevertheless, these risk factors explain only 30-50% of CAD cases [3]. Inherited genomic variation can influence the risk of CAD and provide additional information beyond traditional risk factors [3]. Proteomics, the quantification of circulating proteins, has gained attention as a promising biological layer that complements genomics and can enhance CAD risk prediction [2]. Proteogenomics integrates genomics and proteomics and can deliver additional risk stratification beyond traditional risk factors or either genomics or proteomics alone. CAD screening typically occurs at the population level by measuring traditional risk factors [5]. Given the substantial disease burden and limited explanatory power of traditional factors, providing screening to individuals with elevated proteogenomic CAD risk may deliver substantial benefits [4]. Screening candidates can be identified using a quantitative threshold determined by epidemiological criteria or by defining a target number of candidates. CAD risk-based screening in women is anticipated to have a greater impact than in men. Modelling exercises indicate that an extended proteogenomic risk score for CAD is expected to retain predictive performance as a function of ancestry [6]. Coronary artery disease (CAD) remains the leading cause of death worldwide, with an estimated 18 million fatalities annually. Specific risk-based, stage-based, and adaptive screening guidelines have been established according to sex and age, with distinct advice on further screening or intervention thresholds. CAD severely affects diverse populations, causing excess morbidity and mortality [5]. Currently, no proteogenomic interventions addressing CAD are available for implementation or policy development in any population [3]. Integrating diverse populations into proteogenomic studies will enhance the generalizability of both foundational and stage-based policies and ultimately improve population health, particularly for groups disproportionately affected by disease such as CAD. Implementation is potentially further facilitated by an anticipated rapid proliferation of general population cohorts including diverse ancestries [2].

Risk-Based Screening Paradigms in Coronary Artery Disease

Population-wide screening for coronary artery disease (CAD) can result in substantial benefits for health systems and society at large, but implementing CAD screening at the population level entails important social, ethical, and practical considerations, especially in low- and middle-income countries [5]. Risk-based screening is gaining momentum within clinical and policy arenas as a strategy to foster early intervention for individuals at high risk for future morbidity, mortality, and health-system costs [6]. When screening occurs individually at different ages or ages are specified, but the timeline has not been provided, CAD screening is naturally defined categorically rather than at a set age. Screening in general has ramifications for health equity, and CAD screening is no exception [1]. Evaluating who is captured by screening, when and how screening is conducted, and what follow-on offers are made are all areas in which differences across health systems and populations can either ameliorate or exacerbate inequities when not addressed explicitly [3]. Risk-based screening considers reducing social inequities associated with population-wide interventions that take place at the same age for everyone or early interventions focused only on high-income populations [2]. Population-wide screening introduces greater challenges in consideration of the ethical, legal, and social issues that must be anticipated, addressed, or mitigated at the outset. The exchange of biological samples and the consequent implications for privacy, security, and data sharing are fundamental issues that must be articulated appropriately in each societal context at the point of informing stakeholders about the screening procedure itself [1].

Methodological Framework for Implementation across Populations

Cohort diversity is crucial for the efficient implementation of proteogenomics-guided CAD screening. Therefore, the approach must consider group-specific contexts, values, cultures, and preferences, and emphasize populations historically underrepresented in genomics [1]. Multilayered unconscious biases permeate health systems and impede engagement with diverse cohorts [2]. Overcome barriers by leveraging community-based participatory research to co-design implementation strategies with stakeholder collectives representing underrepresented communities throughout the project lifecycle. Enable knowledge exchange, solicitation of feedback, and capture of insights on specific impediments and facilitators [4]. Proactively seek partnerships with community organizations, non-governmental bodies, and public agencies that align governance with diverse populations' aspirations, priorities, and ownership aspirations [5]. Pilot strategies with underrepresented cohorts and solicit feedback from clinicians, researchers, and patients to identify barriers and enablers specific to each group. Incorporate findings into the wider implementation support framework while maintaining distinct implementation strategies for historically underrepresented groups whose preferences might differ from majority populations [6]. Data sources include standard-of-care clinical data, biobanked samples from legacy research projects, and custom initiatives to gather targeted information from groups often excluded from large-scale biobanking efforts [5]. Eligibility criteria extend to all individuals above 18 years who receive a standard-of-care lipid profile, enabling participation within and outside depository initiatives. Inclusion of longitudinal data on a representative sample of patients with and without CAD in broad pre-symptomatic cohorts remains critical [11]. Efforts are underway to inclusively address the entire spectrum of social and digital determinants of health.

Data Collection and Cohort Diversity

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Risk-based screening for CAD permits early detection and management of an otherwise asymptomatic disease [6]. At the population level, several theoretical models support a targeted approach based on specifically tailored risk thresholds since the majority of individuals are at sufficiently low risk to forgo screening entirely [5]. Risk estimates for CAD are typically derived using traditional risk factors alone, yet presently available proteomic and genomic data can augment traditional metrics through a proteogenomics framework [6]. Additional analyses highlight the need for considerations regarding the diverse populations in which screening programs would be implemented. Variation in ethnic, genetic, demographic, economic, and cultural factors across populations is expected to influence the performance of proteogenomics-guided risk assessment, potentially resulting in a suboptimal clinical yield for any given risk threshold within certain groups[5]. Proteogenomics thus presents an analogous three-layered technical challenge, with the desired epidemiological enhancement centered on the incorporation of diverse populations into CAD-related analyses [5]. Addressing these disparities does not arise from increased precision alone; population-scale upscaling of proteogenomics-linked screening for CAD has the potential to confer substantial additional equity benefits that complement precision efforts, subject to the mitigation of broader social determinants of health for underprivileged groups [6].

Assay Selection and Standardization

An important step for equitable implementation of proteogenomic CAD screening is the selection and standardization of candidate assays [2]. Initially selected for initial screening tests, candidate proteomic assays include strategies for whole proteome, proteome-ome, proteins, and protein fragments; additional identified candidate assays from recent CAD-related genomic studies offer the opportunity to leverage existing genomic resources for a second independent screening test [4]. All assays undergo a process of rigorous analytical validation prior to deployment, with the option for initial on-site testing selected based on specifications and availability of appropriate equipment. Standardized analytical performance for quality control by cross-laboratory proficiency testing is established as a prerequisite for deployment of assays [3]. Where initial on-site testing is not feasible, or when laboratories as a whole lack sufficient capability to undertake the complete validation process, highly portable assays are developed for which complete labelling-free analysis is possible through open-source software, ensuring analytical performance for quality control can be determined and shared[2]. An extensive literature review constitutes a unified, comprehensive overview of existing CAD-related proteomic and genomic cohorts and of the technical performance of established relevant CAD-related assays, enabling exploration of additional sources of data and of the opportunity for a second, independent verification screening test [4]. Analytical performance of candidate proteomic and genomic assays and of analytical procedures can differ intrinsically across cohorts and may also be strongly influenced by environmental factors, equipment, and reagents [7]. Consequently, extensive assembly and comprehensive characterisation of the development cohort represent an essential prerequisite for the building of stable computational models and for their reliable deployment [7].

Computational Integration and Risk Stratification

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, with elevated cholesterol levels being a well-established risk factor for the development of this condition [6]. However, traditional factors such as blood cholesterol levels alone are often inadequate for proper screening, as they are typically distributed similarly between different population groups [6]. For instance, many disease-preventing medications have been developed based on those factors yet have not benefited certain demographics, such as individuals of African descent [5]. Different factors and candidates for risk-monitoring include age, sex, blood pressure, waist-to-hip ratio, prevalent diabetes, and current smoking status. Another possibility to monitor is the concentration of lipoprotein particles, many thereof being secreted before and after treatments, and of blood-based deoxyribonucleic acid (DNA) methylation biomarkers [3]. To predict further test risks, Classical Risk Tools and the Framingham Equations are widely known, and various Artificial Intelligence (AI) models have even been suggested as substitutes [3]. However, with many well-tested and readily available High-Throughput Genomics and High-Throughput Proteomics methods, the consistent integration of genomic and proteomic parameters with health information is preferred, though analysis of how these parameters jointly and temporally interact is still limited[1].

Clinical Pathways and Decision Support

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide 5. CAD is an insidious killer affecting millions of individuals [3]. Atherosclerotic plaque buildup hinders blood flow to the heart, making the condition life-threatening and silent unless assessed [3]. Estimates from the American Heart Association demonstrate that an individual developing atherosclerotic disease has a lifetime risk of 49%, and the current trend seems to evolve adversely, with the possibility of reaching a 69% risk by 2060 [2]. CAD can be classified as stable and unstable. Characterization of CAD into stable and unstable conditions is pivotal. Having stable atherosclerotic disease is not considered equivalent to being screened negative, and the lack of proper

attention to this important notion might hinder the implementation of those screening tools linked to proteogenomic data [6]. The four steps display the methodology assuring that stable and unstable CAD are indeed different health states[6].

Equity Considerations in Implementation

Coronary artery disease (CAD) affects nearly one-third of adults and accounts for 9 million deaths worldwide in 2019, despite widely available preventive interventions [8]. Although screening for CAD risk is a promising avenue for reducing the burden of cardiovascular disease, conventional risk prediction models can produce misleading estimates in certain populations because of limited representation in the underlying development datasets, hindering the effective allocation of preventive resources [9]. Recent advances in proteogenomics, an integrated examination of protein and DNA sequence variation coupled with widespread deployment of plasma proteomics assays, enable the development of population-stratified CAD screening tools that have not yet been implemented in practice [10]. Implementation requires assessing technical feasibility across demographic groups, evaluating the guidance provided by the resulting models, and ascertaining equitable access to screening appointments. Observations from extensive analyses of the public proteomics data collected on the 860,000 Biobank participants, coupled with 20 years of analysis of genetics and health, suggest that deploying models matched to the population group of the individual receiving guidance can enhance performance compared to flexible machines [9]. Moreover, only a modest portion of the overall screening advantages appears to stem from a systematic undersampling of specific race-ethnicity-ancestry groups, especially African American and Chinese. Strikingly, the Biobank datasets indicate that 8–25% of the epidemiology-based guidance provided by even the most fully represented conventional risk factors is not relevant to various population groups [4]. CAD proteogenomics adds a new independent screening dimension and reflects different aspects of the disease, amplifying the potential benefits of implementation and aligning with extensive evidence of the health gaps affecting socially disadvantaged communities [2].

Access, Affordability, and Resource Allocation

The anticipated impact of proteogenomics extends beyond precision medicine, given the substantial population-level burden posed by coronary artery disease (CAD)[9]. Effective risk-based screening approaches have shown promise for balancing population benefits and potential harms [10]. Universal screening remains infeasible in many health systems, including Canada's, due to limited resources and mounting pressures on primary care. Implementing screening protocols that integrate proteogenomics and a core set of classical risk factors may generate significant health gains [10]. Generating and sharing prototypical models trained on diverse populations in different geographic regions could enhance readiness while fostering population-wide equity [9].

Social determinants of health and bias mitigation

Proteogenomics, the integration of genomic and proteomic measurements, has the potential to radically improve population health by identifying individuals at high risk for coronary artery disease (CAD)[7]. Risk-based screening targeting high-risk individuals is preferred over universal screening, but evidence on the societal implications of risk-based screening for CAD is limited [7]. Although nomograms and machine-learning algorithms for CAD risk prediction have been formulated, these approaches remain poorly generalizable outside the populations on which they were trained. Instruments to measure both proteomic and genomic factors have been developed and validated, enabling the construction of the first multi-omic risk-scores for CAD and the exploration of the extent to which these risk-scores are transferable across diverse populations [8]. The interplay between social determinants of health and population-level deployment of proteogenomics-guided screening is acknowledged [9]. The potential effectiveness and equity implications of large-scale screening initiatives depend on both the availability of scalable, rapid assays that deliver analytical validity in resource-poor settings and the extent to which implementation considerations addressing potential bias and inequities are anticipated and built in from the outset of planning [2].

Community Engagement and Stakeholder Collaboration

Proteogenomics is the study of how biological variations in a genome are translated to changes in proteins and ultimately to changes in phenotype [11]. It integrates genomic and proteomic data to deepen understanding of complex biological questions, including the molecular basis of rare diseases, cancer, and the development and progression of polygenic diseases, to inform risk-based CAD screening strategies[13]. In addition to traditional risk factors, other biological processes contribute to the pathway to atherosclerotic cardiovascular disease, several of which are regulated by genomics at the individual level and can be measured with proteomics [13]. Biomarkers involved in inflammation, lipid metabolism, reverse cholesterol transport, hemostasis, and renal function have been associated with CAD [8]. Large epidemiological studies across multiple populations have established causal roles and differential effects for many of these processes on CAD, demonstrating the critical importance of population representation for accurately assessing proteogenomic risk [8].

Evaluation and Outcomes Monitoring

Accountability and progress monitoring are essential for any implementation effort. The following goals, therefore, underpin the design of the implementation plan [7]. First, the detailed framework specifies the analytical validity, clinical validity, and clinical utility of proteogenomics-guided risk-based screening for CAD [5]. Second, since widespread deployment is desired, the implementation plan includes health outcomes, particularly MACE and mortality over the long term, as well as equity metrics. Benchmarks will inform progress in achieving these endpoints. Finally, principles of implementation science and learning healthcare systems will guide the approach to monitoring, evaluation, and iteration [8]. A further objective is to establish interoperability with a comprehensive set of contemporary genomic, proteomic, and other health-sector data, in line with evolving definitions of digital data, electronic health records, interoperability, and a catalogue of data provenance to track stakeholders and record version modifications [8]. Reporting formats conform to established standards, analyst- and dataset-specific preparatory procedures are transparent yet analogue, and specification of technical, clinical, and any other thresholds is assured. Structures for audit trails, reproducibility in practice and reporting, and continuity in transfer of intellectual property, and other rightsgovernance accompany a standardised risk-score catalogue of data provenance to track stakeholders and record version modifications [6]. Reporting formats conform to established standards, analyst and dataset-specific preparatory procedures are transparent yet analogue, and specification of technical, clinical, and any other thresholds is assured [5]. Structures for audit trails, reproducibility in practice and reporting, and continuity in transfer of intellectual property, and other rights [1].

Analytical Validity, Clinical Validity, and Utility

Risk-based screening for coronary artery disease (CAD) aims to identify individuals at greatest need of early detection and preventive intervention [10]. Proteogenomics informs such screening by integrating multi-omic predictors of risk across the lifespan, augmenting established factors like age, sex, lipid levels, diabetes mellitus status, and smoking history [11]. Predictees may include low-density lipoprotein cholesterol, apolipoprotein B, pulse-wave velocity, fibronectin, complement component 3, and matrix metalloproteinases that together remain clinically opaque yet expose biological pathways implicated in CAD. Screening models comprising diverse populations can better inform screening policy while addressing inequities arising when tools are developed solely in predominating cohorts [12]. Diverse populations are less represented in studies evaluating CAD screening, yet stand to benefit from integration of proteogenomics into preventive programs [11]. Implementation should proceed iteratively, studying implementation milestones and practical preparedness across populations before engagement broadens. Discernment of readiness by approving bodies, as well as potential gains from the intervention, motivates such fractional advancement [12].

Health Outcomes and Equity Metrics

Proteogenomics-guided risk-based screening for coronary artery disease (CAD) offers pivotal opportunities to inform equitable implementation across diverse populations [1]. Initial performance assessments of a proteogenomics-augmented CAD screening algorithm have identified pronounced disparities in model performance among different populations, suggesting opportunities to bolster equity-oriented benefits [3]. To exploit these potential opportunities and lower the risk of exacerbating historical inequities in preventive care, empirical evidence is required to evaluate model performance in diverse populations, and guidance is needed to implement a screening approach that incorporates equity considerations as a core design criterion. Continual review of health outcomes, equity metrics, and implementation science indicators will enable a learning health-system approach that allows for timely adjustments and refinements [4]. Health outcomes and equity metrics will be rigorously monitored to evaluate theoretical and empirical health-system impacts of CAD proteogenomics on population health and health equity. Three overlapping sets of endpoints are prioritized: analytical validity, clinical validity, and clinical utility [7]. Health outcomes and equity metrics will be reviewed regularly across different clinical contexts and health systems. Targeted follow-up studies are planned to monitor CAD proteogenomics impact on disparate populations, and community-level initiatives will address barriers to equitable access in settings where socioeconomic disparities are pronounced [6]. Implementation science frameworks will guide monitoring efforts to capture knowledge on adoption, effectiveness, cost, and other dimensions of implementation [8, 2]. Two simple approaches are envisaged to benchmark health-outcomes and equity measures against community-tailored targets. Comparison with diverse settings that are implementing universal screening under enriched epidemiological and financing conditions will inform screening demand and adoption potential across broader health systems needing implementation-shared knowledge [8]. Theoretical and empirical foundations for risk-based screening frameworks conditional on age and additional factors have been described [9]. In addition to population-level benefits, the models highlight that many individuals with elevated risk may not have high enough likelihoods to trigger the minimal biomarker-investment threshold for universal initiation, whereas systematic risk-targeted action on surrounding screening opportunities may offer considerable value[10].

Implementation Science Frameworks and Learning Health Systems

Genomic applications that hold the potential to improve population health by identifying high-risk individuals may inadvertently exacerbate health inequities if they are not made accessible to all groups. Innovative genomic interventions are at risk of being underexploited because the U.S [6]. The healthcare system lacks effective implementation strategies to integrate them into routine practice. Implementation science frameworks, which can enhance the uptake, sustainability, and impact of genomic screening technologies across diverse health systems, remain underutilized [7]. Furthermore, implementation science has addressed only limited aspects of genomic screening, and the social and behavioral science frameworks that could help support equitable implementation have not been systematically applied [7]. Strategies to improve outreach, engagement, and education about screening remain poorly developed, particularly those that are grounded in an equity lens [8]. The implementation of proteogenomics-guided screening for CAD presents a compelling opportunity to leverage established principles from implementation science to support equitable rollout across diverse populations, thereby maximizing the likelihood of success [9]. The Consolidated Framework for Implementation Research (CFIR), which is widely used for planning and evaluating innovations in health care, offers a structured approach best suited to specifying the steps necessary to achieve comprehensive implementation [5]. Three primary objectives underlie the equity-focused plan for screening deployment. First, the effort will characterize and document systematic differences in the epidemiology of CAD and the performance of CAD risk models across diverse populations and subgroups. Second, the initiative will develop a standardized and interoperable implementation blueprint that health systems worldwide can tailor to local needs and contexts [7]. Third, the approach aims to ensure that the broad set of outcomes evaluated encompasses not just health, but also equity in health access, resources, processes, and outcomes [2, 5].

Ethical, Legal, and Governance Considerations

On the scale of health-related variables, privacy is one of the most sensitive. Protecting individual health data is crucial to comply with international legal frameworks such as the General Data Protection Regulation (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA) in the European Union and the United States, respectively [13]. To this end, robust mechanisms to ensure data privacy, confidentiality, integrity, and the right of withdrawal should be put in place, alongside appropriate consent models and the possibility of the return of results across selected populations [15]. Governance mechanisms should guarantee that the use of data is specific, transparent, and trustworthy, enabling authorization to be secured more effectively [3]. A strong interplay exists between regulatory requirements and quality assurance, and the governance structure and capability profile of multiple health systems in tandem with the clinical and organizational context, population, domain of implementation, and risk and opportunity analysis [5]. Delivery models that incorporate decision support can benefit from expertise, reputation, capacity, and understanding, and this network can help formulate policies aligned with business objectives. Coordination should facilitate outreach to external international entities and the structure of training capacity that can support local adaptation without excessive duplication [7]. Verification and quality assurance should encompass accepted standards from relevant organizations, depending on the regulatory classification of the implementation [8].

Data Privacy, Consent, and Governance across Populations

Considerable variation in how populations perceive acceptable levels of data privacy and control over research participation is common, even when information is anonymized [13]. For example, individual governance is often difficult in settings where research consents have been provided through general proposals for using biomaterials in study protocols [12]. In such instances, commonly proposed strategies include institutional review board (IRB) approval of secondary use with detailed plans articulated in documents intended for participating individuals, or allowing participants to choose between two options with differing governance [14]. Other governance options under consideration include general dynamic consents, biobanks, return of results procedures, checks on discriminatory use of data, and mechanisms that recognize the intellectual contributions of populations while still protecting individuals [11]. The principles and practices of governance for research participation should thus be continually revisited across populations that yield data, and an engagement framework is recommended to reflect these considerations [10]. Emphasis on mitigation strategies is warranted, given ongoing doubts expressed by health experts regarding fairness in the development, validation, and deployment of risk assessment tools. Delegates at the World Health Organization Global Summit on Artificial Intelligence Research and Development and the 2023 Global Forum on Artificial Intelligence for Humanity in Canada have issued warnings that existing algorithms may discriminate against certain population subgroups when predicting health indicators such as breast cancer [15]. Such scrutiny highlights the need to anticipate anomalies arising from risk-adjusted analysis of health data collected under diverse clinical and governance conditions across different populations, and to adopt practical methods of informing preclinical populations about probable delays in implementation [15].

Regulatory Pathways and Quality Assurance

Proteogenomics represents an integrated approach that combines the genome, epigenome, transcriptome, and proteome to uncover the mechanisms that drive complex biological phenotypes and different diseases [8]. CAD is a complex and heterogeneous disease influenced by environmental, genetic, and biological risk factors. Traditional risk factors are not sufficient to detail the full spectrum of CAD vulnerability [7]. Specific plasma proteins measured by high-throughput proteomics underpin CAD pathophysiology and are independent of traditional risk factors. These determinants, together with targeted genomic variants associated with variability in the maturation of these proteins, can provide an improved stratification of CAD risk across diverse populations [8]. Performance and clinical usefulness are expected to differ, entailing increased uncertainty on which populations to prioritize [5]. When applied to hundreds of thousands of individuals, the model generates risk scores whose distribution can be visualized across the globe, revealing points of divergence, including that certain regions remain out of the domain of applicability of the model, as shown in representative figures [7]. More extensive exploration of the value of proteomics to the early identification of CAD risk in a large set of populations remains essential to ensuring at-risk individuals can be targeted for preventive interventions such as dietary changes, increased physical activity, cessation of smoking, and avoidance of pollutants [6, 5, 2].

Transparency, Accountability, and Patient Autonomy

Data governance frameworks for proteogenomic risk-based screening must prioritize transparency and accountability [2]. Clinicians and patients require a clear understanding of the evidence underpinning the screening approach to make informed decisions and ensure meaningful consent [4]. The persisting social stigma surrounding coronary artery disease (CAD) amplifies these needs: individuals may choose to forgo life-saving interventions based on societal perceptions; transparent communication regarding risk stratification is therefore essential [3]. Governing bodies have assorted social contracts, and obligations to the public extend beyond data governance. Stakeholders across the proteogenomic consortium should regularly communicate the overarching rationale for the program, its progress toward addressing these aims, performance across diverse cohorts, and feedback on co-developed decision-support tools [8]. Periodic updates through community-engagement mechanisms will maintain awareness and transparency and capture perceptions or concerns at local stages.

Policy Implications and Scalability

Coronary artery disease (CAD) accounts for approximately 9.4 million deaths annually, making it a leading cause of morbidity and mortality worldwide [15]. Establishing CAD risk is thus of paramount importance for clinical guidance and health policy. It is feasible to screen symptomatic or asymptomatic individuals based on their risk, yet little guidance exists on whether a universal or a risk-based screening model is more appropriate [12]. Risk-based screening admits greater flexibility in defining eligibility and the nature of the intervention, along with the possibility of significantly reduced investments in programme implementation, health system capacity, and health consequences for the population as a whole [3]. Frameworks exist for determining universal versus risk-based screening as well as for establishing risk thresholds for deciding who to screen [6]. Theoretical perspectives indicate that all else being equal, population-wide prevention strategies could bring greater population-level benefits and smaller population-level health consequences than risk-stratification approaches [3]. However, empirical studies of these models consistently highlight that the positive impact of universal screening is hugely contingent on overall major-COA CD risk, and that both theoretical and empirical assessments of universal and risk-based screening hinge critically on expected health gain [7]. Such broad reflections suggest that there would be high value in exploring clinical models and health settings in which CAD screening is already established, and that focusing on one level of abstraction (decision frameworks) should therefore give way to developing an additional level of intensity in describing screening-monitoring–assessment–decision–implementation pathways[8]. CAD is widely regarded as a highly significant global health issue, with an estimated 17 million deaths attributed to it annually [10]. The impact of CAD varies markedly from one population to another, with adjustment for conventional population-level factors such as Gross National Product (GNP) revealing stark differences in burden across populations [15]. Variations are similarly pronounced in risk-factor profiles and, similarly, in the cellular mechanisms through which risk factors exert their influence [16]. Against this theoretical backdrop, the first two conditions of the CAD population vary substantially both across geopolitical macroregions and within those macroregions; excessive emphasis on investigating additional populations in a state of early-stage refinement has been established [15]. Therefore, the broad choice of a diverse yet widely distributed set of CAD-afflicted populations and a specific focus on the initial exploration of microregion-level extractions within the high-CAD-setting Punjab region represent justified pathways for accelerating the processes of articulation and accumulation of knowledge irrespective of an a priori base of information concerning the CAD population to be studied[16].

Reimbursement Models and Health System Integration

Many high-impact preventive services in the health system remain inadequately covered by reimbursement models [10]. Coronary artery disease (CAD) screening is now recommended by several organizations for certain

at-risk groups. Early data suggest that proteogenomic-based risk prediction can help stratify individuals along the CAD spectrum and target screening to those at the highest risk [16]. The business case for clinical implementation remains to be made, particularly the appropriateness of leveraging a cardiovascular generative artificial intelligence (AI) solution already integrated into electronic health records (EHRs). Current "decision range editor" measures external perceptions on AI output within clinical environments; CAD screening in early 2024, therefore, provides an opportunity to assess added value beyond standard proteogenomic-guided screening with potential ongoing economic engagement [7]. One approach to promote standardized and risk-based implementation of proteogenomics across diverse populations and mitigate unintended bias is to embed this within a general 'digital twin' deployment that captures organization-wide simulated evidence on proposed modelling approaches and broader analysis of external and internal data flow [6]. The central focus is on transparency, equity, and extension of protection against bias. Key steps include population-level risk assessment of screening initiatives; the potential economic return from specific applications; and the evaluation of model performance across different environments and under varied mechanistic and training data assumptions [4]. The risk of bias arising from diverse organ offering between calibration and application populations is notable and supports a precautionary approach to modelling and comprehension before screening deployment.

Workforce Training and Capacity Building

The growing complexity of healthcare innovations demands enhanced capacities among the entire workforce engaged in the relevant healthcare paradigms [8]. Workforce needs vary substantially in different healthcare systems and sociocultural settings [5]. The implementation of proteogenomics-guided risk-based screening for CAD must thus account for diverse use cases and prioritize workforce training and capacity development in ways that reflect the science, technology, and practice underpinning these use cases [3]. Efforts to implement health innovations, including the use of novel screening technologies, often encounter barriers that must be recognized and planned for. Implementation frameworks can advance the consideration of relevant factors [3]. For example, the Consolidated Framework for Implementation Research (CFIR) identifies five overarching domains (characteristics of the innovation, the inner setting, the outer setting, the individuals involved, and the implementation process), along with 39 specific constructs associated with successful implementation [2].

International Collaboration and Knowledge Transfer

Knowledge transfer and international collaboration can facilitate the advancement of proteogenomics-guided risk-based screening for CAD in diverse populations [16]. The discipline of networked genomics, which encompasses knowledge-sharing across borders, can enhance the transfer of know-how pertaining to community engagement, laboratory workflows, ethical frameworks, and analytical methods [11]. Embedded enrichment of cohorts can also improve the exploration of population-specific screening challenges and the co-development of solutions. The greatest potential for knowledge co-development and transfer exists with countries that exhibit shared cardiovascular health challenges or possess specific expertise of potential relevance [10]. Proteogenomics-guided screening for CAD aims to engage communities throughout the design, validation, and implementation stages, and such efforts should consider the social determinants of health and their interplay with the risk factors related to CAD. Since CAD is a pressing issue for many Caribbean nations, the Caribbean Public Health Agency is ideally positioned to lead a collaborative initiative [9]. Symposia, workshops, and regular consultations involving a diversified group of stakeholders, including governments, regulatory agencies, academia, and civil society, can be instituted to refine understanding of community needs, preferences, knowledge, cultural contexts, and additional determinants of health relevant to this population [8].

Case Studies and Practical Exemplars

To guide equitable implementation of proteogenomics-informed risk-based screening for coronary artery disease, exemplary practices and lessons learned from existing initiatives can support systematic planning and broad engagement with diverse communities [13]. A portfolio of representative case studies illustrates how proteogenomics guides population screening deployment across life-course stages, health conditions, and geographic contexts. These programs share the overarching aim of harnessing the capacity of omics-based biospecimen analysis to enhance individual-level risk identification and motivate preemptive care [10]. Detailed information on candidate community-embedded studies is summarized, highlighting success factors, encountered challenges, and mitigation strategies conducive to equitable engagement with vulnerable populations [15]. Accompanying structured templates enable prospective implementers to adapt the proteogenomics screening framework, evaluate local needs and opportunities, estimate potential outcomes, and develop implementable proposals for consultation and collaboration [12]. Engagements with health authorities and programmes focused on chronic disease prevention, commencement of analysis on broad-spectrum proteomic screening across diverse populations, and exploration of cryopreserved biospecimens to extend outreach serve as additional strategies for equitable adoption of molecular biospecimen and multi-omics analyses [8].

Future Directions and Research Priorities

Proteogenomics promises to transform CAD risk-based screening by adding predictive power to risk models that incorporate established clinical factors and targeted population-specific measurements [12]. Proteogenomics models like the Stanford Cardiovascular Health Score, which combines established risk factors with proteomic features collected mainly from diverse, underrepresented cohorts, have demonstrated markedly improved CAD stratification among broad populations and specific ancestry groups compared with genomics-only approaches [13]. A recent study indicated that a proteogenomics-guided cardiovascular health score outperformed both traditional and genomic-only risk models in CAD prediction across diverse US settings, reinforcing the clinical need for population-representative studies to validate proteogenomics-guided screening more widely and monitor equity impacts. Implementation Foundation Building upon a robust evidence base for proteogenomics-guided CAD screening, continual integration of scientific advances into operationalization efforts enables systematic, equitable progression from protective theory to preventive practice [14-18]. Scientific progress tracking within a concerted action plan fosters timely knowledge capture, minimizes redundancy, and maximizes productivity [15]. The implementation framework is informed by ongoing, substantive contributions from diverse stakeholders, including intergovernmental organizations, foundations, research institutions, health systems, and industry, during both strategy formulation and active strategic development phases. Capacity enhancement and barrier mitigation measures are in constant review against emergent realities, and collaborative avenues are continuously scouted for augmentation of hundreds of ongoing partnerships [19-22].

CONCLUSION

Proteogenomics-guided risk-based screening offers a promising pathway to improve early identification and prevention of coronary artery disease by integrating multi-omic biomarkers with clinical and environmental risk factors. Its potential lies not only in enhancing predictive accuracy but also in enabling more efficient and targeted allocation of preventive resources at the population level. Nevertheless, successful implementation across diverse populations requires careful attention to cohort representation, assay standardization, computational transparency, ethical governance, and equitable access to screening services. Embedding implementation science principles, stakeholder engagement, and continuous evaluation of health and equity outcomes will be critical to translating proteogenomic advances into real-world practice. With sustained international collaboration, robust validation across populations, and policy frameworks that prioritize fairness and accessibility, proteogenomics-guided screening can contribute meaningfully to reducing the global burden of coronary artery disease while advancing equitable precision public health.

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