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Precision Public Health Applications of Multi-Omic Risk Scores for Chronic Kidney Disease: Evidence, Equity, and Implementation Challenges

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ABSTRACT

Chronic kidney disease (CKD) represents a major and growing global public health burden, with substantial proportions of cases remaining undiagnosed until advanced stages. Emerging precision public health approaches leveraging multi-omic risk scores, integrating genomic, epigenomic, proteomic, and metabolomic data offer significant promise for improving early detection, risk stratification, and targeted prevention strategies. This paper examines the current evidence base supporting the use of multi-omic risk scores in CKD, highlighting their potential to enhance predictive accuracy beyond conventional clinical models and enable timely, individualized interventions at the population level. Despite these advances, substantial challenges remain in translating multi-omic risk scoring into routine public health practice. Key implementation barriers include limited external validation across diverse populations, inadequate health system infrastructure for data integration, and unresolved questions regarding clinical utility and actionability. Equity concerns are particularly salient, as underrepresentation of diverse populations in omics datasets risks exacerbating existing health disparities, while unequal access to testing and care may skew benefits toward more advantaged groups. Ethical and governance considerations including data privacy, consent, and fair data use further complicate large-scale deployment. Addressing these challenges requires a coordinated, interdisciplinary approach that integrates methodological rigor, inclusive data generation, robust governance frameworks, and health system readiness. Strengthening population diversity in datasets, improving interoperability of health data systems, and aligning policy and funding mechanisms will be essential to ensure equitable and effective implementation. Ultimately, multi-omic risk scores have the potential to transform CKD prevention and management within a precision public health framework, provided that scientific innovation is matched with ethical, equitable, and context-sensitive implementation strategies.

Keywords: Chronic kidney disease (CKD), Multi-omic risk scores, Precision public health, Health equity and Implementation science.

INTRODUCTION

All-cause chronic kidney disease (CKD) affects over one in ten adults worldwide, is the eighth leading cause of death, and is associated with increased risks for cardiovascular disease and various cancers [1-6]. Systematic reviews estimated that up to 60% of CKD cases in high-income countries and up to 65% in low-income countries remain undiagnosed [7-12]. The pathophysiology of CKD involves several physiologically distinct biosignatures across multiple biological domains, specifically, epigenomics, genomics, metabolomics, and proteomics, that could inform CKD risk scores based on multi-omic data [13-19].

Background: Multi-Omic Risk Scores and Chronic Kidney Disease

Chronic kidney disease (CKD) affects 10% of the global population and is projected to be the third most prevalent cause of death by 2040 [20-27]. It occurs in several primary forms, mainly diabetic kidney disease, aging, systemic hypertension, glomerulonephritis, and polycystic kidney disease [28-34]. A universal framework classifies CKD based on time course, etiology, pathophysiological abnormalities, and morphological lesions [35-42]. Most CKD risk tools like the Framingham cardiovascular disease risk score, the Framingham heart study 30-year coronary heart disease risk score, and the American college of cardiology, and American heart association risk score achieve poor discrimination and calibration due to these factors [43-48]. Technologies such as multi-omics enable better mechanistic understanding of the disease. A systems perspective contextualizes CKD restoration strategies within the broader network of nutrient consumption, energy welfare, waste elimination, homeostasis, and integrity reinforcement. Addressing unjust health inequities, such as access to multi-omic profiling and fair distribution of intervention benefits and burdens, is therefore critical for a socially accountable precision public health agenda [49-54].

Evidence Base for Multi-Omic Risk Scores in CKD

CKD represents a major health burden globally and an important target for population-level risk mitigation. Multi-omic risk scores aim to estimate an individual's risk of developing CKD based on modeling relationships among CKD, a range of multi-omic biosignatures, and standard risk factors [55-60]. Enriching standard models with multi-omic information can markedly enhance CKD risk stratification, thereby identifying individuals who would benefit most from periodic monitoring of kidney function, lifestyle modification, or pharmacotherapy aimed at preventing or delaying CKD progression [61-64]. The hypothesis that population-wide implementation of multi-omic risk scores for CKD would significantly reduce incidence and progression of the disease rests on the premise that the biosignatures and risk factors used in population models or algorithms should be relevant across all population strata [4].

Equity Considerations in Precision Public Health for CKD

The deployment of multi-omic risk scores for CKD is framed explicitly within the priority area of precision public health [5]. The objective is to enhance population health by advancing the understanding of fundamental biological processes associated with disease susceptibility, hence informing the identification of individuals at high risk and facilitating targeted interventions where they are likely to be most effective[5]. The motivation for applying these tools to the prevention of CKD stems from the high and rising burden of the condition in the United States and the consequent appeal of scaling up preventive efforts [6]. Population-based studies indicate that, despite the clarity of the inverse relationship between risk and income, targeted interventions tend to skew towards high-income individuals, thereby exacerbating existing disparities [7].The urgent need for CKD prevention is emphasized by data on the condition's prevalence, incidence, and mortality, the risk of progression following diagnosis, and the adverse outcomes associated with kidney failure and ESRD [9]. The aim is to motivate the prioritization of efforts to promote effective CKD prevention within precision public health. Population-level modeling illustrates that multi-omic risk scores indeed have the potential to change the conversation from a focus predominantly on screening and early diagnosis to a wider consideration of prevention [10].

Population Diversity and Representation

Scientific justification for applying precision preventive approaches to chronic kidney disease (CKD) posits that improved population health hinges on identifying individuals at higher risk [4]. Predictions based on multi-omic risk scores have emerged as a leading strategy, harnessing abundant and disparate data sources. A remaining question concerns the translation of scientific evidence into practice [5]. More than one billion people globally are estimated to be affected by CKD, with over 80 million cases classified as stage 3 or higher, foreshadowing an impending public health crisis [6]. Population diversity shapes the construction and calibration, and thus the performance and applicability, of predictive models [7, 8]. For example, multi-omic risk scoring schemes are informed primarily by non-Hispanic White (NHW) individuals, who are overrepresented in corresponding pooled discovery and biobank datasets [9]. In contrast, substantial reliance on genomics and other molecular data invites risk stratification in populations underrepresented in large observational cohorts. Models based on such data, moreover, may have low generalizability if developed without monitoring population characteristics. CKD risk scoring studies with biobank data typically encompass only NHW participants [10]. The current overview indicates that multi-omic risk scores for CKD have been validated in independent studies but using only NHW populations or individuals residing outside the United States, the United Kingdom, or European Union. Claims for generalizability to non-NHW populations remain unsubstantiated [11]. Calibrated risk estimates, prediction boundaries, and clinical implications may thus vary. In Keller, tested multi-omic risk models nevertheless provided actionable insights for certain demographic subgroups. Ongoing attention to population diversity is warranted throughout the implementation of multi-omic risk scoring for CKD [12]. Population diversity also shapes

delivery of preventive service. Data from the 2019 Commonwealth Fund Biennial Health Insurance Survey indicate that routine screening for diabetes, hypertension, and high cholesterol varies across multiple dimensions, including income, insurance status, education, and race[12]. Access to multi-omic testing for CKD risk scoring, likewise, is likely to encompass social determinants of health.

Access and Benefit Distribution

Precise risk-score-based stratification for multi-omic data remains at an early stage in chronic kidney disease (CKD), and slow fully scaled development continues to question how bio-signatures and signals can provide benefits shaping preventative measures and course of action on populations at risk [4]. Access to testing, coverage, affordability, and distribution of benefits shape who has priority to entertain such new preventive measures and this area commands attention across implementations [5]. Early-onset CKD, as well as advanced stage progression, are amplified by social determinants of health, upstream neighbourhood factors, and associated background social vulnerability [6]. Tight conditioning of the scoring mechanisms to locus position could increase risk accuracy, yet at the potentially increased peril of ameliorating or eliminating signals of upstream systemic vulnerabilities arising before or beyond specific concerned loci. An equitable procedure of tractable augmentation with these background CCGE should be generated, delivered early and widely for extra consideration [7].

Social Determinants of Health and Contextual Factors

Chronic diseases, as framed by the World Health Organization (WHO), are defined as diseases of long duration and slow progression [2]. The WHO further maintains that chronic diseases are not only of long duration but also comprise pathology that may advance over a long period without any clinical symptoms [3]. The list of chronic diseases included in the WHO chronic disease denotation includes: Cardiovascular diseases (CVD), Cancer Chronic respiratory diseases (COPD, Asthma, etc.), Diabetes Chronic Kidney Disease (CKD) is not considered a chronic disease by the WHO [3]. The occurrence of kidney disease and CKD may occur following acute stages like Acute Kidney Injury [4]. CKD prevalence is reported to be rising at an alarming rate especially in areas in the world where better access to health care, better nutrition, and health awareness is on the rise[5]. The WHO reports that approximately 10% of the world's population is affected by potentially life-threatening chronic kidney disease (CKD) [6, 10]. CKD represents a growing public health risk and a major contributor to the increasing international burden of non-communicable diseases (NCDs)[9]. Current CKD screening targets high-risk groups based on demographic and clinical risk factors. Although these factors are common, a substantial proportion of patients who develop CKD and eventually progress to end-stage renal disease (ESRD) lack such conventional risk factors at the time of screening [10]. These observations raise the critical need for improved CKD screening methods that can alleviate the public health threat of CKD and simultaneously address growing cardiovascular risk and health equity. Multi-omic risk scores combining genomic, proteomic, metabolomic, and epigenomic biosignatures are emerging as precision risk evaluation tools for a variety of diseases 1. Multi-omic risk scores for stratifying individual population-level CKD risk and anticipating CKD progression from early-stage disease can empower precision public health efforts targeting CKD [11]. The establishments of multi-omic risk scores for CKD compatible with community-engaged approaches, ensuring cultural and contextual relevance, represent a high-impact precision public health opportunity [12].

Implementation Challenges for CKD Risk Scores

The application of risk scores or algorithms that integrate multiple data types (multi-omics) to chronic kidney disease (CKD) within a precision public health framework faces several implementation challenges [4]. These challenges comprise technical integration, data governance, clinical utility, and workforce development [4]. Many health care organizations seeking to incorporate new tools into practice turn to integration platforms that facilitate embedding risk scores into electronic health record (EHR) systems [4]. These platforms help define workflow, interoperability, and technical requirements. Generalizable factors shaping the successful integration of CKD algorithms into health systems remain poorly understood. Building on firsthand experience gained from clinical collaborations, a strategic approach to technical integration emphasizes four key aspects: health system integration, data governance, clinical utility, and workforce development [5].Health systems may also evaluate how to embed score delivery directly into EHRs, which should support clinician adherence by providing real-time information at the point of care. Collaboration with stakeholders can help define integration and reporting options tailored to specific needs[5]. Complex algorithms like CKD multi-omic risk scores may involve extensive data preparation and analytic infrastructure that limit inter-operability and workflow identification [5]. Implementing new tools often requires establishing compatibility across diverse EHR vendors with varying data availability. When determining whether CKD risk scores would benefit a health system, stakeholders consider the complementarity of available tools and the priority assigned to kidney health relative to other focal points [6]. Interest may be driven by the increasing fragility of population health, the heightened vulnerability of certain demographic groups, and the importance of chronic illness and comorbidity in understanding population

determinants. Health systems with existing CKD initiatives and multisectoral participation supporting kidney health, equity, and social determinants may be particularly well positioned [7].

Technical Integration into Health Systems

Organizational benefits accrued from an efficient electronic health record (EHR) adoption are difficult to anticipate without a data-driven approach [4]. Adopting automated systems without the assurance of business value through related key performance indicators can produce suboptimal investment return. Multi-omic risk scores might accelerate approval among large health systems by providing a clinical imperative to facilitate this clinical business case and fulfilling institutional goals of enhancing population health [5]. Multi-omic datasets, comprising genomics, epigenomics, proteomics, and metabolomics, expand risk modeling across biological pathways and application horizons, rising to a second prevention tier extending pre-CKD focus to end-stage renal disease (ESRD) multisystem complications to improve scalable pathways toward system integration[8]. The corroborative use of these large datasets merits rapid assessment during early evaluation to ascertain calculable populations for CKD and ESRD. Migration toward integrated health systems has increased the value of timely risk-score dissemination and the incorporation of concomitant multi-omic datasets [9]. Automation through EHR systems reduces waiting periods and patient reliance on informatics personnel, facilitates enduring assessments across folio systems, and liberates larger resources for cross-institutional implementation move-from-back-end-to-front-end objectives to refine risk-score, pathway-target-system population caps [11].

Data Governance, Privacy, and Ethical Considerations

Health systems are increasingly generating and collecting genomic and multi-omic data at large-scale population levels across diverse contexts to evaluate novel use cases and address practical challenges [3]. The NDHM initiative in India, for instance, seeks to integrate individual health and demographic data through an interoperable digital system, and gene panel testing for hereditary conditions is being offered to broad cohorts of Indian patients with actionable results becoming available to public health agencies [4]. Multi-omic data across 16 diverse health systems are being collected for systematic reviews of biological mechanisms underlying long-COVID and other adverse aftereffects of SARS-CoV-2 infection [11]. Despite these advances, unresolved privacy, consent, security, and confidentiality concerns create barriers that hinder further engagement and uptake [1, 12, 13]

Clinical Utility, Decision Thresholds, and Actionability

Multi-omic biosignatures for chronic kidney disease (CKD) stratify risk among individuals classified as low and moderate risk by conventional clinical tools [2], enhancing prevention prioritization and enabling early interventions that avert or delay progression. Evidence supporting clinical utility, however, remains limited [1]. An analytical framework co-develops multi-omic models with population-level interpretations of risk, evaluates implementation feasibility, and informs choices about broad cohort inclusion that diversify utilization contexts and enhance generalizability [9]. Following similar application to coronary artery disease and atrial fibrillation determinants, consideration for CKD extends the approach and supports cross-disease collaboration [13]. Clinical actionability hinges on the capacity to influence patient trajectories towards strikes and outcomes, yet CKD risk score specifications lack consensus [14]. Proposed follow-up actions include population education on CKD and its sequelae, exploration of tailored screening modalities or biorepository engagement, and examination of reversible factors that promote progression. Prioritizing communication about actionable information, risk dimensions, and personal relevance empowers individual decision-making and refines cohort specifications [15].

Workforce Training and Interdisciplinary Collaboration

Considerable workforce training is needed for widespread uptake of multi-omic CKD risk scores in public health, but a coordinated interdisciplinary effort across medicine, bioinformatics, and public health can enable this integration [10]. One clear direction is to provide public health practitioners more education, training, and hands-on experience working with data analysis tools and data science concepts [11]. Such instruction would empower professionals to better inform design and evaluation of data science initiatives as CKD risk scores are developed and deployed. For medical education, efforts can focus on enhancing the data science content of existing programs as well as on encouraging data science skill building during advanced training [10, 11]. Instruction across the biocuration field offers another avenue to enhance CKD risk score-oriented collaborations and adjacent activities.

Policy and Governance Implications

Adoption of precision public health interventions for chronic and progressive diseases is generating new policy, funding and governance considerations [1]. Regulatory clarity on datatypes and analytical approaches needed to inform decision-making can facilitate efficient risk stratification [15]. Multi-omic risk score analysis is grounded in material or active determinants of health and importantly addresses multi-level governance needs [2]. Geospatial neighbourhood mapping can support equitable distribution of interventions and build upon existing measures of sectoral equity to account for safety, the built environment and the urban heat island effect 12 and to understand exposure-mediation [16]. Safe use of multi-omic data requires broad institutional leadership and

commitment to the principles of fair data use throughout progressive risk stratification policy development, funding decision-making and support for commercialisation and scale [17].

Methodological Considerations and Evaluation Frameworks

To foster the proactive identification and prevention of chronic kidney disease (CKD) across the population, population-based multi-omic risk scores aim to predict incident CKD and its progress toward kidney failure or cardiovascular events in the general adult population [8]. These risk scores summarize an individual's lifetime risk of developing CKD by integrating information from multiple omic biosignatures (proteomic, metabolomic, genomic, or epigenomic). Multi-omic biosignatures are independently associated with the initiation and progression of CKD [15]. The development and validation of these scores support upstream interventions necessary to implement proactive health strategies within the precision public health framework [16]. Building upon the prior foundational evidence around lifelong accumulation of CKD risk and population-based approaches, the CKD consortium establishes a complex system biology model based on the current understanding of CKD initiation and progression [10]. This model maps disease exposures and risk biosystems from multi-omics to the population-based intervention-building effort [11]. The biosystems are then transformed to biosignatures that are very early, upstream or latent, obtainable from relatively easy (non-invasive, low-cost, fast, widely available), and common tests, forming the basis of CKD population risk stratification. An implementation framework integrates interventions identified at the population level into health systems [12]. The concern for precision in public health is with the correct population to receive the CKD risk scores and follow-on interventions towards maximum health gain distribution. This approach aligns with a precision implementation public health framework that estimates how much and when the risk scores can benefit the population and the individual [12]. Generally, multi-omic risk-scores for CKD are also expected to reduce health inequities by ensuring the biological causes of CKD risk in diverse populations are captured while protecting against universal approaches that do not reflect population differences [13]. The delivery framework intends that diverse populations in both training and application data gain and high health benefits can be achieved, consistent with a long-standing goal of the Centre for Microbiome and System Medicine [1].

Case Studies and Lessons Learned

Multi-omic risk scores for chronic kidney disease (CKD) show promise but present methodological gaps and subtle epidemiological nuances [14]. Understanding these considerations remains crucial for designing precision public health strategies that maximize health benefits and minimize harms for different populations [14]. Case study of multi-omic risk scores for CKD identifies transferable lessons and highlights equity, implementation, and governance priorities for similar initiatives targeting other diseases or risk factors [15].

Future Directions and Research Priorities

Despite considerable progress, several critical research priorities can accelerate the adoption and maximize the precision public health potential of multi-omic risk scores applied to chronic kidney disease (CKD)[17]. Addressing these priorities will strengthen the underlying evidence base, refine the accompanying methodologies, and further sharpen the equity-focused agenda [16]. Substantial evidence supports CKD-associated multi-omic risk scoring in different populations and clinical contexts, yet rigorous external validation for CKD detection and monitoring remains limited [10]. Methodological advances that promote transportability and generalizability will enhance the predictive performance of standard tools [1]. Approaches that combine multi-omic data with electronic health record information including medication history, comorbidities, and clinical visit frequency could facilitate enhanced collaboration and elucidate population-specific characteristics influencing pathophysiology and risk scoring [9]. Large general populations and diverse at-risk populations, where CKD prevention and management warrant greater focus, remain under-studied. Collectively, these factors motivate research into techniques, risk-drivers, and populations [10, 16]. Multi-omic data-science platforms represent an innovative space of opportunity across a broad range of applications. Further exploration of complementary data-science disciplines such as artificial intelligence, deep learning, time-to-event analytics, and shape analysis could yield high-impact insights into CKD multi-omic risk scoring and into CKD prevention, management, and associated applications [17]. Additional risk-horizon analytics that characterize and reveal the evolving temporal-neighborhood of multi-omic measurements could strengthen population-health, even community-health understanding. Further methodological explorations could also unite the more established health-impact-assessment field with contemporary multi-omic applications for instance, by predicting future incident events on the basis of diverse environmental and observational factors [17].

CONCLUSION

Multi-omic risk scores represent a transformative advancement in the prevention and management of chronic kidney disease, offering the potential to shift public health strategies from reactive treatment toward proactive, precision-based prevention. By integrating diverse biological data with traditional risk factors, these tools can improve early identification of high-risk individuals, enhance stratification accuracy, and inform targeted

interventions that may delay or prevent disease onset and progression. However, the translation of multi-omic risk scoring from research to real-world public health application remains constrained by significant scientific, ethical, and systemic challenges. Limited generalizability due to underrepresentation of diverse populations, gaps in clinical validation, and uncertainty regarding actionable thresholds undermine confidence in widespread adoption. At the same time, disparities in access to testing, infrastructure limitations, and workforce capacity gaps risk reinforcing existing inequities if not proactively addressed. To realize the full potential of multi-omic risk scores, future efforts must prioritize inclusive research design, robust validation across heterogeneous populations, and the development of clear clinical and public health pathways for action. Investments in digital health infrastructure, workforce training, and interoperable data systems will be essential for effective integration into health systems. Equally important are strong governance frameworks that safeguard privacy, promote transparency, and ensure fair distribution of benefits. In conclusion, while multi-omic risk scores hold considerable promise for advancing precision public health in CKD, their success will depend on a deliberate and equity-centered implementation approach that bridges the gap between technological innovation and population health impact.

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