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Editorial

Implementation of genetic tests for disease prevention: challenges in evidence synthesis across clinical utility domains

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Robust evidence supports the critical role of genetic risk in shaping the frequency of a broad range of diseases, underscoring its significance as a determinant of health outcomes [1]. Accordingly, genetic and genomic tests hold significant potential for disease prevention by stratifying populations based on individual genetic profiles and guiding targeted interventions. However, despite the enthusiasm surrounding these technologies, their integration into preventive healthcare faces significant hurdles, primarily due to the insufficient evidence supporting their clinical utility [2]. Clinical utility, though not universally defined, generally refers to the test's usefulness to provide actionable information that improves health outcomes.

Demonstrating clinical utility involves proving the clinical efficacy of an intervention, following a test, in reducing the health burden of the condition for which it is used and proving that it can be implemented through the analysis of other dimensions including acceptability, organizational feasibility, costs, and the impact on health inequalities [2]. The gold standard for evaluating clinical efficacy is a randomized controlled trial that assesses the effectiveness of a personalized preventive intervention incorporating genetic or genomic tests alongside the standard of care. However, due to the challenges involved, requiring direct empirical evidence of clinical outcomes may not always be feasible or necessary when comparing the efficacy of personalized approaches with traditional preventive strategies. A more nuanced approach, evaluating each case on its own merits, may be needed. In some situations, evidence of clinical validity may suffice, such as in high-penetrance genetic disorders where preventive interventions for the chronic disease have already proven effective. In other cases, the most effective strategy might be to use non-inferiority trial designs in high-risk populations or to employ intermediate endpoints, whose correlation with disease incidence or mortality is well-supported by evidence. The use of simulation models to evaluate the impact of these preventive approaches on hard outcomes is also a topic of ongoing debate, as their results can provide valuable insights [3]. However, their reliability depends on the quality of the supporting data, the robustness of assumptions, and the accuracy of the models used.

Given the complexity of evaluating the evidence required for implementing genetic and genomic technologies, a collaborative approach involving expertise in epidemiology, clinical practice and public health is essential. In 2021, the European Union approved a new Health Technology Assessment (HTA) regulation aiming at streamlining the assessment process, allowing EU Member States to jointly assess the clinical evidence for new technologies. While the regulation does not yet explicitly cover genetic and genomic tests, a standardized approach that requires evaluation of the key clinical dimensions at the European level could significantly streamline the decision-making process for the adoption of genetic tests in prevention.

However, the application of the new EU HTA regulation to genetic and genomic technologies might not be sufficient, as assessing clinical utility requires a broader perspective that goes beyond cost-effectiveness to encompass the evaluation of all the dimensions that affect the real-world effectiveness, such as acceptability or feasibility. Although these evaluations are formally required within HTA frameworks, they are frequently overlooked, leading to recommendations that fail to account for the full implications of implementing these tests in healthcare systems [2]. Furthermore, it is key that the health impact of prevention policies or programs that use genetic-based technologies is prospectively evaluated, to generate evidence supporting the wide implementation of such policies. In this context, integrating Health Impact Assessment (HIA) to evaluate the broad public health effects of a policy, which includes the assessment of equity factors like accessibility and feasibility, will enhance decision-making [4]. Overall, HTA and HIA will contribute to the design of more effective strategies tailored to the specific characteristics of populations.

A key strength of HIA lies in its structured stakeholder engagement, which ensures that diverse perspectives are captured, making the outcomes more relevant and widely accepted. In the context of personalized prevention, this process can account for factors such as varying access across socioeconomic groups and geographical areas which, coupled with differences in health literacy of citizens and patients and trust in healthcare systems, can exacerbate existing disparities and influence who benefits from these technologies [5]. Furthermore, HIA helps policymakers identify the necessary policy measures for the effective implementation of prevention strategies, including reimbursement models and infrastructure investments, tailored to the specific needs and challenges of national healthcare systems. In addition, HIA supports the creation of robust implementation programs that incorporate continuous monitoring and adaptation, ensuring that policies can evolve in response to new evidence and the ever-changing healthcare landscape.

In conclusion, while genetic and genomic tests hold great promise for advancing disease prevention, their integration into healthcare

systems requires a comprehensive approach to evidence synthesis. The application of the new EU HTA regulation to genetic and genomic testing represents a step forward in streamlining assessments; however, further efforts are needed to ensure that the health impact of policies that effectively implement these technologies is well addressed. This requires a collaborative approach involving all relevant stakeholders and the establishment of continuous monitoring and improvement plans to ensure their long-term sustainability in health systems.

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