PROPHET

a PeRsOnalized Prevention roadmap for the future HEalThcare

STRATEGIC RESEARCH AND INNOVATION AGENDA (SRIA) ON PERSONALISED PREVENTION

First Draft

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Deliverable Abstract
This First Version of the SRIA will include the conceptual model for integrated, multilevel precision prevention (defined in the Concept Paper), as well as identified typologies and case reports identified.

Keywords
Strategic Research and Innovation Agenda, Personalised Prevention, Personalized Medicine, Public health genomics, health policy, health technology assessment, health impact assessment, PROPHET framework, clinical utility, clinical validity, genetic testing indicators

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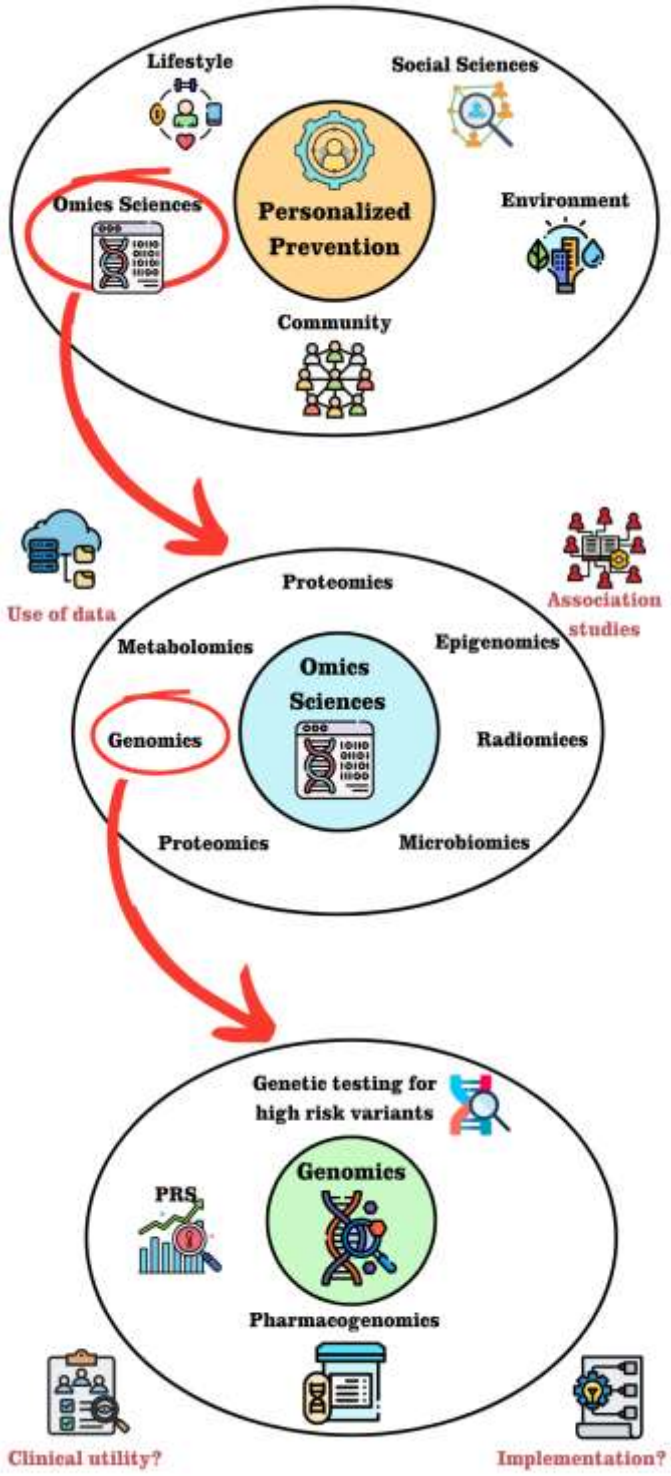
1. Executive Summary

The PROPHET Strategic Research and Innovation Agenda (SRIA) on Personalised Prevention reflects on the challenges for advancing personalised prevention in healthcare. With PROPHET, we are building the foundation to achieve the **final outcome** of **more effective, efficient and citizen-centered preventive approaches.** After extensive literature mapping on the latest research advancements in the field and after incorporating the consortium partners' views and the stakeholders' perspectives, the SRIA identified ten challenges for the implementation of personalised prevention, and a number of actions to overcome them.

Along the development of PROPHET, personalised prevention clearly emerges as a multi-faceted field that seeks to use individual information from various domains as safely and effectively as possible. This information includes an individual's lifestyle, health records, social habits, environmental exposures over time, individual omics data, role in the community, and more. Recognizing this, PROPHET endorses and strongly promotes this comprehensive definition of personalised prevention. However, to ensure the sustainability of evidence-systematization efforts, it was decided to focus on managing omics data within this ecosystem. This strategic decision aligns with the project's positioning within the International Consortium for Personalised Medicine ecosystem. Thus, while this SRIA acknowledges the importance of these diverse domains in defining personalised interventions, it primarily concentrates policy development efforts on investigating the omics sciences sector.

Figure 1. The PROPHET ecosystem

Within this defined domain, we encounter additional complexity due to the multiple areas covered by omics sciences — such as genomics, metabolomics, proteomics, radiomics, epigenomics, and more. Despite their technical differences, certain shared elements allow us to propose common considerations across these fields, particularly regarding infrastructures required for omics data use. Issues related to data collection, integration, protection, and the development of data infrastructures thus have broad relevance across omics domains (Figure 1).



In contrast, when digging deeper to seek evidence of clinical utility that could inform implementation and scaling up by healthcare systems, the situation varies. In many areas of omics, there is a clear need for new, robust association studies to support biomarker candidacy as potential tools for personalised prevention. However, genomics stands out as the most structured in terms of implementation.

Given its early entry into scientific focus compared to other omics, genomics offers the primary examples upon which PROPHET has built its considerations around clinical utility and implementability, where examples of such utility are available, albeit with limitations. These examples form the core objectives of this SRIA, including applications such as genetic testing for high risk pathogenic variants, polygenic risk scores (PRS), and pharmacogenomics. These

applications highlight the practical aims of this initiative and serve as focal points for advancing personalised prevention through clinically actionable genomics data.

In conclusion, PROPHET represents a significant step towards a future where prevention is truly personalised at all its' levels, empowering individuals to take control of their health and well-being. The SRIA outlines the major areas that must be addressed in order to fully realize the potential of personalised prevention .

2. Background and methodology

2.1 Definition and Vision: why is personalised prevention important?

The "*Health at a Glance: Europe"* report serves as a stark reminder of the overwhelming prevalence and impact of chronic diseases on the continent.[1] As these diseases continue to be the leading causes of morbidity and mortality, accounting for a substantial proportion of premature deaths, the burden on healthcare systems becomes increasingly apparent. Moreover, the socio-economic implications of chronic diseases, including diminished productivity and increased healthcare costs, highlight the urgency for innovative and sustainable solutions.

These elements pose a direct threat to the sustainability of European healthcare systems. The traditional reactive model of healthcare, focusing on treating established diseases, is proving to be economically unsustainable. As such, a transformative shift towards primary prevention and early diagnosis, together with more effective use of pharmacological therapy, is imperative for achieving a balance between effectiveness, efficiency and quality within the constraints of public budgets.

In the past two decades, advancements in sequencing and genotyping technologies and the integration of digital resources in healthcare have ushered in a new era of medicine. This "precision-revolution" has opened possibilities for personalised prevention, where individualised risk profiles are identified through a nuanced understanding of genetics, behavioural and socio-economic factors. By tailoring interventions based on this information, personalised prevention aims to delay disease onset, enhance quality of life and ultimately reduce the economic burden on healthcare systems. In this context, the need for a comprehensive and proactive strategy to mitigate the burden of chronic diseases is more pressing than ever. This Strategic Research and Innovation Agenda (SRIA) delves into the intricacies of the personalised prevention paradigm and elucidates the reasons for its crucial integration into European healthcare systems.

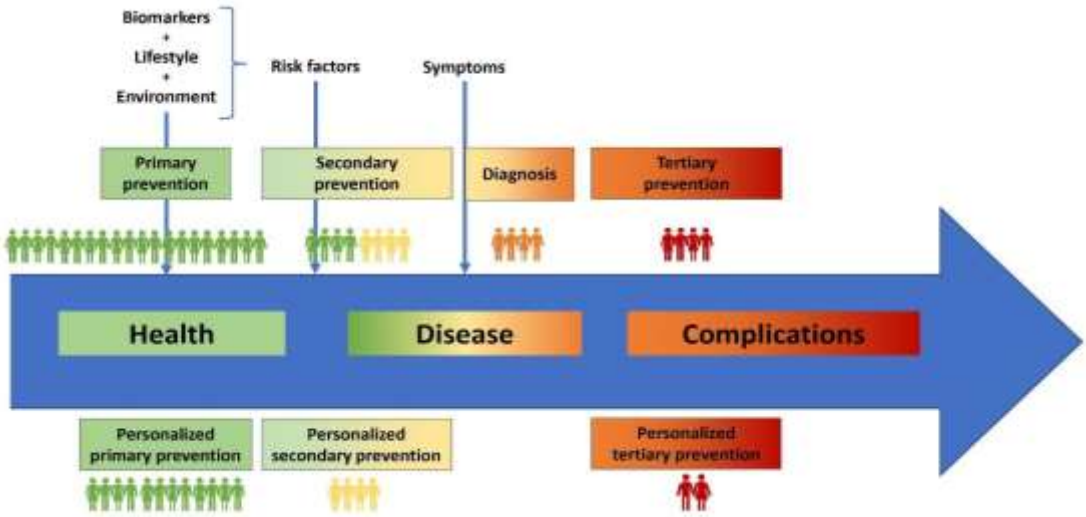
The personalised PREvention of Chronic DIseases (PRECeDI) consortium, established in 2019, laid the groundwork for the integration of personalised prevention into chronic disease.[2] It emphasized the potential of preventive interventions targeting high-risk individuals and underscored the need for

parallel changes in healthcare systems, while highlighting the large gap between therapeutic offerings and prevention tools in the field of personalised medicine.

By leveraging these premises, the "*A personalised Prevention Roadmap for the Future Healthcare*" (PROPHET) project aims to bridge these gaps by advocating for a holistic approach that considers not only solid biomedical knowledge but also economic sustainability, policy alignment and investments in cutting-edge technologies. PROPHET is a Coordination and Support Action of the International Consortium for Personalised Medicine (ICPerMed) and it involves 18 partners from 12 EU Member States, and the UK.

During the kickoff meeting of PROPHET in September 2022, personalised prevention was conceptualised as a targeted approach considering biological, environmental and behavioural characteristics, along with socio-economic and cultural context (*"personalised prevention aims to prevent onset, progression and recurrence of diseases through the adoption of targeted interventions that consider the biological information (e.g., genetic and other biomarkers, demographics, health conditions), environmental and behavioural characteristics, socio-economic and cultural context of individuals. This should be timely, effective and equitable in order to maintain the best possible balance in lifetime health trajectory").*[3] Various terms, such as Precision Prevention or Precision (Public) Health[4], are used interchangeably, emphasizing the need for precision and effectiveness in health promotion. The Fig. 2 depicts our vision of the three levels of personalised prevention in PROPHET.

Figure 2. Description of the three levels of prevention, according to the disease stage.



Initiatives like PReCEDI and PROPHET chart a course towards the integration of personalised prevention into the fabric of European healthcare. The transition from reactive treatment models to proactive and individualised preventive measures holds the promise of a healthier and more sustainable future for all people across the continent. Embracing personalised prevention is not just a choice: it is a necessity for building resilient and effective healthcare systems that can withstand the complex health challenges of the 21st century.

2.2 PROPHET expected outcomes

The PROPHET project anticipates a spectrum of far-reaching outcomes and impactful contributions, strategically aligned with the overarching mission to innovate healthcare through the implementation of Personalised Prevention as an integral part of the current traditional approaches in prevention.

PROPHET employs a structured methodology, including the creation of a Stakeholder Platform, literature mapping, research gap analysis and the development of the PROPHET Framework. The outputs are disseminated through targeted communication strategies and capacity-building activities to maximize the impact of Personalised Prevention strategies across various stakeholder groups.

These expected outcomes encompass a multidimensional approach, addressing various domains and stakeholders, with a profound emphasis on sustainability, innovation and societal well-being.

Main expected outcomes are:

1. Comprehensive Personalised Prevention Roadmap
2. Strengthened Collaborative Ecosystem
3. In-Depth Research Advancements
4. Evaluative Frameworks and Indicators
5. Empowered Public Health Authorities
6. Raised Awareness among Citizens, Patients and Healthcare Professionals and Citizen Engagement
7. Informed policy makers thanks to Policy Briefs and Communication Strategies

A detailed description of expected outputs and outcomes is set out in Table 1.

In summary, the expected outcomes and impact of the PROPHET project extend beyond the development of a Roadmap; they encompass a holistic transformation of healthcare practices, stakeholder collaborations, research advancements and societal awareness.

The project's endeavors are poised to pave the way towards a future where personalised prevention is not just a concept but a tangible and integral component of healthcare excellence.

Table 1. PROPHET Goals, activities, main outputs and expected outcomes.

	Goal	Activities	Main Outputs	Expected Outcomes
Foster Collaboration, comprehensive personalised prevention Roadmap for effective prevention and Strategic Research and Innovation Agenda	Establish a comprehensive personalised prevention Roadmap. Establish collaboration among stakeholders in the field of personalised Prevention for the creation and implementation of a SRIA.	Create a Stakeholder Platform, to engage key stakeholders in order to contribute to the SRIA on personalised Prevention, to inform research funders and prospective partners. Develop a detailed Roadmap outlining actions, output and results indicators.	A Stakeholder Platform, a structured mechanism for SRIA co-creation and a comprehensive SRIA translating PROPHET's vision into a long-term systemic approach.	1. <u>Comprehensive personalised Prevention Roadmap</u> This accompanies the SRIA and details the actions and timelines by which this SRIA is expected to be implemented. The Roadmap provides a detailed blueprint for implementing tailored preventive strategies for each individual, based on the latest scientific advancements and the specific needs of each context. 2. <u>Strengthened Collaborative Ecosystem</u> A relevant activity of PROPHET is to strengthen the collaboration network among all stakeholders involved in the field of personalised prevention, aiming to create a robust and sustainable ecosystem.
Research Advancements in personalised Prevention	Gain a thorough understanding of research advancements in personalised Prevention through literature mapping, research gap analysis and mapping existing funded projects and programs.	Conduct literature mapping, research gap analysis and mapping of existing research projects and programs for personalised Prevention in Europe and beyond.	Mapping reports of the existing scientific literature in the domains of personalised Prevention.	3. <u>In-Depth Research Advancements in personalised Prevention</u> Literature mapping, research gap analysis and mapping of recent research projects and programs are expected to yield insightful reports in the domains of personalised Prevention. These outputs will not only inform the development of the personalised Prevention Roadmap but also contribute to the broader scientific community, advancing knowledge and guiding future research initiatives.
Provide instruments to evaluate the Effectiveness and Clinical Utility of	Assess the clinical utility, key success factors and gaps of current personalised preventive	Conduct literature reviews on the evaluation frameworks used to appraise omics	Analysis of adoption of approaches in all domains, identification of facilitators / barriers	4. <u>Evaluative Frameworks and Indicators</u> A significant outcome of the project is the establishment of evaluative frameworks and indicators for personalised Prevention approaches. Through a meticulous analysis of existing bottlenecks, success factors

personalised preventive approaches	approaches. Identify bottlenecks, analyze evidence and evaluate successful implementations.	technologies and extract the indicators to evaluate the relevant domains of clinical utility.	and a list of indicators to evaluate personalised Prevention approaches.	and barriers, PROPHET will identify key process and outcome indicators. These indicators will serve as essential tools for assessing the clinical utility and scalability of personalised preventive approaches, providing a tangible contribution to evidence-based healthcare practices.
Strengthen Public Health Authorities	Analyze how personalised Prevention can be delivered most effectively, efficiently and cost-effectively. Design a multidimensional framework (the PROPHET Framework) for appraising and adopting personalised preventive approaches.	Develop the PROPHET Framework and apply it to assess existing personalised prevention programs. Provide Capacity Building activities for Policy Makers and Health professionals through dedicated tool boxes and residential and educational efforts	The PROPHET Framework, 3 case studies and 4 Action Plans for personalised Prevention programs and Capacity Building activities.	5. <u>Empowered Public Health Authorities</u> The project aims to empower Public Health Authorities by providing them with a multidimensional framework for designing, assessing and implementing personalised preventive approaches. This framework, integrated into the SRIA, is expected to be a practical resource for policymakers and health authorities, enhancing their capacity to navigate the complexities of personalised Prevention and make informed decisions that benefit public health.
Raise Awareness among Citizens and Patients	Raise awareness among public and patients on the potential of personalised Prevention to improve quality of life. Engage them in defining, establishing and adopting personalised preventive services.	Implement awareness campaigns, capacity building for public and patients and develop tailored communication tools.	Guidelines for public and patient engagement, policy briefs and communication strategies tailored to stakeholders. Delivery of training courses, targeted awareness campaigns	6. <u>Raised Awareness among Public, Patients and Healthcare Professionals and Patient Engagement</u> The project aims to empower individuals to actively engage in their health journey. This outcome extends to a broader cultural shift, where a patient-centric approach is encouraged, fostering open dialogues between health professionals, patients and their families.

			and capacity-building activities.	
Raise Awareness among Healthcare Professionals and Stakeholders	Raise awareness among Health Professionals, Life Sciences Companies, Insurers, Regulators and Policy Makers. Promote collaborative relationships for the quick adoption of personalised Prevention approaches.	Stakeholder involvement via the Stakeholder Platform, awareness campaigns and capacity building for healthcare professionals.	Guidelines for stakeholder engagement, policy briefs and communication strategies tailored to targeted stakeholders.	Raised Awareness of healthcare professionals and policy makers Through the elaboration of a policy brief and tailored communication strategies, PROPHET aims to influence decision-makers, ensuring that the insights and recommendations derived from the project are disseminated effectively. This outreach is designed to catalyze policy changes that align with the vision of integrating personalised Prevention into the fabric of healthcare systems.

2.3 Building on lessons learned

One of the fundamental theoretical underpinnings of PROPHET is the "Vision Paper on Personalised Medicine Research & Implementation by 2030" by ICPerMed, a comprehensive and forward-thinking approach that envisions the integration of personalised prevention strategies as a fundamental element in the evolution of healthcare for all the public[5]. This vision is based on the idea that tailoring medical interventions to individual characteristics, including genetic, environmental and lifestyle factors, holds the potential to significantly enhance the effectiveness and efficiency of healthcare delivery.[6]).[7] ICPerMed was created in 2015, bringing together over 50 European and international partners, working as a "think tank" focused on Policy and Strategy for Personalised medicine and on fostering Internationalization and Global cooperation. Over the past 10 years, ICPerMed produced several key documents to foster research and implementation in Personalised medicine, including an Action Plan (https://www.icpermed.eu/activities/action-plan/; 2017) and a ICPerMed's Vision 2030 reflects a concerted effort to engage a wide array of stakeholders, including experts from diverse professional backgrounds and sectors, to ensure that the implementation of personalised medicine is both inclusive and impactful. The emphasis on personalised prevention approaches within this vision aligns with the broader goal of empowering individuals to actively participate in maintaining their health and well-being. By integrating personalised prevention into the fabric of healthcare, ICPerMed envisions a future where individuals are equipped with the knowledge and tools to make informed decisions about their health, thereby contributing to improved health outcomes on a societal level. Furthermore, the ICPerMed's vision emphasizes the need for a paradigm shift in healthcare systems to accommodate the principles of personalised medicine. This includes fostering an environment that supports the responsible use of health-related data. By placing personalised prevention at the forefront of its vision, ICPerMed acknowledges the potential of these strategies to not only improve individual health but also to contribute to the sustainability and resilience of healthcare systems as a whole.[8]

2.3.1 Promising stories in personalised prevention

In the countries where top level scientific expertise and universal countrywide coverage of health insurance and medical services are supported by forward-looking and timely established legislation, inspiring examples have been set as outgrowths of public-private partnership. To illustrate a real-life solution already in practice in a thoroughly investigated topic[9], tailoring individual recommendations

for breast cancer screening, Polygenic Risk Score (PRS)-based earlier surveillance, availability of further testing for high-risk gene variation if needed, and qualified medical assistance at hand mark the basic steps to personalised prevention and care in this area where delayed activities can cost lives. Additionally, targeted analysis of specific patient pathways from prevention and pre-diagnosis to recovery or end-of-life care brings together key stakeholders from various sectors and effectively identifies key development needs, which can then be prioritized based on their importance and feasibility[10].

Making a change in paradigm takes time – however, this statement should not postpone the first steps to be taken as soon as possible. As an essential prerequisite to build a solid basis for a country-wide personalised medicine system, the medical and related data management must meet the highest level security standards, yet perform fluently. In Estonia, this is called the e-Health system. Its main success factors are clear governance, legal clarity, a mature ecosystem, agreement about access rights, and standardization of medical data and data exchange rules[11]. Consequently, more than 20 years of a general population biobank (EstBB, part of BBMRI-ERIC netwrok of biobanks) have created transversal competences in science, medical practices and healthcare governance both locally and internationally. The experience from several pilot projects carried out using the wide spectrum of the scientific capacities of EstBB[12] [13] now serve as examples of how far the best outputs from a biobank can reach to, and accelerate the medical practices in Estonia and elsewhere.

Biobanks in several countries have started to return results of findings with implications for care and prevention. Pilots have been done and are ongoing on how best to deliver such information. For instance, participants can be contacted by the biobank or access their results via a portal Estonian Biobank Launches Portal to Deliver Genetic Results to Biobank Participants - Research In Estonia. Frontiers | A Web Portal for Communicating Polygenic Risk Score Results for Health Care Use—The P5 Study (frontiersin.org). Lessons from the Estonian biobank include participant reactions to such results and ways to deliver these results via counselling, which may prove to be time consuming.[14]

In Finland participants can access their own 10-years absolute disease risk estimate of Type 2 Diabetes, based on traditional risk factors, such as BMI and cholesterol measures and PRS. Participants can compare their own total risk with a matched age population, their projected risk at age 60, and calculate changes to their risk if they would make lifestyle changes , such as stopping

smoking. Such tools may help participants understand their own role in improving their health and promote citizen empowerment.

The P5.fi Study, based on Finland's FinHealth 2017 population-based study, assessed how individuals responded to personalized genetic risk information and its influence on health behaviors. Focusing on polygenic risk scores coronary artery disease, type 2 diabetes, and deep vein thrombosis risks, it provided biobank donors with secure, personalized reports of the genetic and total risk for these diseases. Relevant pharmacogenetic and single variants for the diseases were likewise analyzed and the results returned. The study provided lifestyle guidance and information about the diseases and genetics through the MyP5 website. Participants' responses and health outcomes were monitored over years to evaluate the feasibility of integrating genomic data into public health, aiming to address challenges in applying predictive, preventive, and personalized health approaches. https://thl.fi/en/research-and-development/research-and-projects/the-p5.fi-study-genetic-information-for-health-support[15]

The GenomeHealth project, a collaboration between Finnish hospital biobanks, aims to integrate genomic data from biobank samples into healthcare to advance personalized medicine. The study utilizes the genomic data created by the Finngen-study (www.finngen.fi). By screening high-risk genes like BRCA1, BRCA2, and PALB2 for cancer susceptibility, the project developed a streamlined process for delivering significant genetic findings to biobank donors. The variants selected to be screened in the project are well-known, and there are clear action models and treatment recommendations for them, including enhanced follow-up, preventive surgery, and targeted therapy such as PARP inhibitors. Utilizing the MyBiobank digital service, donors were contacted and, with consent, informed of their genetic risks, then referred to clinical services for further testing and counseling. This approach not only supports early disease intervention but also demonstrates cost-effectiveness, highlighting Finnish biobanks' potential in preventive healthcare. Also cost-benefit analyses of the approach are being done.[16]

The vast majority of both the studies participants were satisfied with the provided services. On top of health benefits, these studies as well as previous research showed that analyses of biobank samples can be done very cost-effectively, and in some cases, even saving costs.[17]

2.4 Synergies with other initiatives

During the different stages of project development, PROPHET will make contact and synergies with numerous initiatives.

First, PROPHET is fully matched and aligned in purpose with the Europe's Beating Cancer Plan, reflecting a resolute political commitment to comprehensively combat cancer. The plan is structured around key action areas and provides a holistic approach, addressing the entire spectrum of the disease pathway, from prevention to treatment and emphasizing the improvement of the quality of life for cancer patients and survivors. PROPHET's activities are intricately aligned with the nuanced Roadmap of action 31.2, the "Roadmap to personalised Prevention", making a substantive contribution to the overarching goals of the Europe's Beating Cancer Plan.[18]

The project supports personalised prevention within the cancer, that can serve as blueprint for successful initiatives in other chronic diseases, and extends its influence on pivotal European initiatives, notably collaborating with*e* ICPerMed and the *European Partnership for Personalised Medicine* (EP PerMedEP PerMed was launched on October 5, 2023, marking a significant milestone in advancing research in personalised medicine across Europe., EP PerMed rallied 60 partners to contribute to its development, with the primary goal of advancing innovative personalised medicine approaches in healthcare systems. EP PerMed's initiatives are underpinned by the SRIA for personalised medicine published in 2023[19], another key document useful in the construction of PROPHET's SRIA. This collaborative synergy enriches the landscape of personalised medicine, contributing significantly to the realization of a fortified European Health Union characterized by resilience, preparedness and sustainability in the face of evolving health challenges.

The concept of personalised prevention inevitably relies on the availability of data that allows for the individualization of healthcare interventions, as well as the creation of infrastructures that enable data sharing in a manner compliant with high European standards for both the effectiveness of healthcare systems and the protection of citizens' and patients' privacy and data security. To address these needs, the European Commission has funded three initiatives/projects: in 2018, the *1+Million Genomes (1+MG)*[20] initiative was launched. Twenty-six European countries have signed the declaration, aiming to enable secure access to genomic and corresponding clinical data across Europe for better research, personalised healthcare, and health policy making. In 2020, the *Beyond 1 Million Genomes (B1MG)*[21] project was initiated, focusing on the goals of the design and testing phase of the 1+MG Initiative. B1MG produced the 1+MG Framework (https://framework.onemilliongenomes.eu/about-

the-framework) a user-friendly interface to navigate the guidelines and recommendations of the 1+MG initiative. Subsequently, in 2022, the *Genomic Data Infrastructure (GDI)*[22] project began. This €40M co-funded project builds on the preparatory work of the 1+MG working groups, the B1MG project, and investments from EU countries. The GDI project is enabling access to genomic and related phenotypic and clinical data across Europe by establishing a federated, sustainable, and secure infrastructure for data access. Both projects are coordinated by ELIXIR, which acts as a neutral broker for the 1+MG countries and aims to sustain biological infrastructure to support the initiative's ambitions. The *Genome of Europe* project also supports the 1+MG initiative and started in October 2024. The project will build a European network of national genomic reference cohorts of 1,000,000 citizens, selected to be representative of the European population.

Lastly the *Transforming Health and Care Systems* (THCS) European Partnership, co-financed by the European Commission under the Horizon Europe Research and Innovation Framework, stands as a noteworthy initiative supporting personalised prevention advocated by PROPHET. By backing coordinated national and regional research, innovation programs, capacity development and networking, THCS actively contributes to the transformation of healthcare and care systems across Europe. In facing common challenges, healthcare and care systems in Europe necessitate harmonised solutions and THCS serves as a strategic opportunity to unite stakeholders and facilitate the digital transformation of healthcare services. With a goal to transition towards more sustainable, efficient, resilient, inclusive, innovative and high-quality healthcare and care systems, THCS aims to generate new knowledge, co-design solutions and strengthen healthcare systems through diverse activities.

The collective commitment of PROPHET and other initiatives enriches the landscape of personalised medicine, paving the way for a future where individualised healthcare becomes a cornerstone of the European healthcare system.

In conclusion, the integration of the results from different projects and initiatives is crucial to implement personalised prevention at European level and beyond.

2.5 Mission: the need of a SRIA on personalised prevention

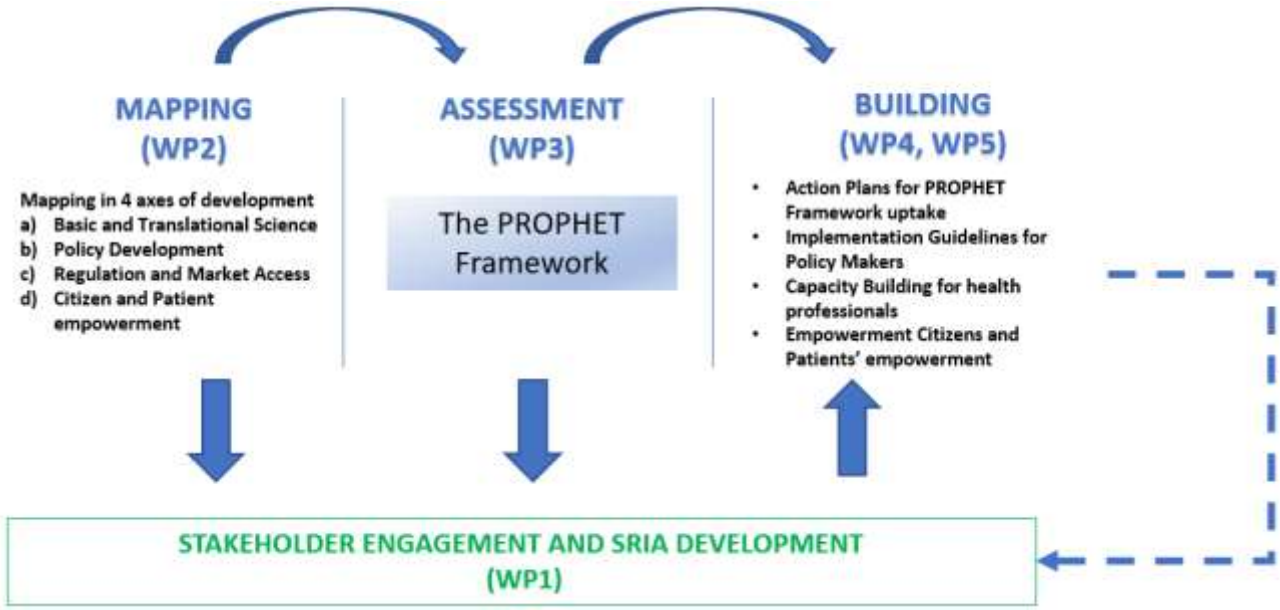
The current document aims to support EU Member States when scaling up personalised preventive approaches for primary, secondary and tertiary prevention, interweaving the levels of biomarkers, individual behavior, and environment/societal factors. Unlike the traditional *one-size-fits-all* approach, which applies the same preventive measures to everyone, personalised prevention focuses

on tailored interventions based on individual health profiles and risk factors. By considering the outcomes listed in Table 1, this SRIA seeks to address the key elements required to ensure that personalised prevention strategies are effectively implemented and that their benefits are realized across Europe.

2.6 Methodology for SRIA development

The SRIA is grounded in a highly multidisciplinary construction model, integrating the consortium's vision for personalised prevention (summarised in a Concept Paper described in 2.6.1), and the assessment and synthesis of various project outcomes through a co-creation process ensured by robust stakeholder engagement. In terms of evidence, the SRIA draws from all three major phases constituting the PROPHET approach: **Mapping**, which involves extensive research on the state of personalised prevention in Europe and beyond; the **Assessment** process, built around the PROPHET Framework, that provides decision-makers with a path and related indicators to evaluate personalised prevention approaches before implementation; the **Building** phase that presents results from the actual implementation of the PROPHET methodology in diverse health and social contexts. The stepwise approach for SRIA development is depicted in Figure 3.

Figure 3. The approach for SRIA development in PROPHET.



*WP1: Work Package 1

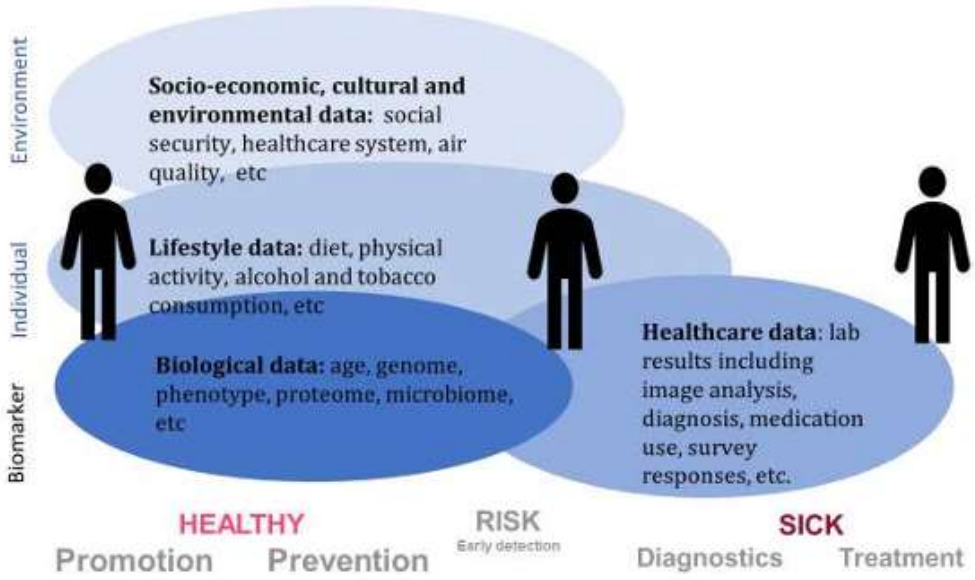
2.6.1 The PROPHET Concept Paper

Efforts from the first year of activities of PROPHET have been summarized in a Concept Paper[23], which served as the foundation for the full Strategic Research and Innovation Agenda (SRIA) in the field of personalised prevention. This document encapsulates the consortium's vision, definition, and initial insights regarding the gaps and challenges of personalised prevention that need to be analyzed for its implementation. The Concept Paper has been informed by preliminary results of literature reviews, mapping analyses, and input from a wide range of stakeholder and key informant interviews and consultations at European and national levels.

The paper defines personalised prevention and its links with previous European initiatives in personalised medicine. It highlights PROPHET's role and the SRIA as a tool to support the implementation of innovative, sustainable, and effective personalised programs to prevent common chronic diseases in all European Member States. Precision in interventions implies predicting and addressing risk (at scale), in individuals as well as groups of individuals sharing different characteristics. Here the high-risk vs the population (subgroup) approach needs to be balanced recognizing Rose's prevention paradox[24]. In essence, effective public health prevention must strike a careful balance between precision targeting for high-risk groups and broader measures for the general population. This trade off depends on how much risk is confined to an identifiable population group, and the extent to which precision can be achieved in identifying this group and addressing this increased risk. This is likely to vary across risk factors and diseases, and across socioeconomic groups. And whether these groups have access to health and social services.

The project's strategy involves engaging the broad health ecosystem and addressing individual risks within a community context, especially for primary prevention in healthy individuals (Fig.4). Data plays a central role in this approach, categorized into three subsections in PROPHET: biomarker, individual lifestyles and environmental/contextual factors. The disease and life-course stages, ranging from healthy to sick, involve actions across promotion/primary prevention, secondary prevention and tertiary prevention/treatment level.

Figure 4. Potential source of information needed to achieve precision and personalization of prevention and treatment across the life course.



The Concept Paper also preliminarily identified preliminary challenges that constitute the core of the PROPHET project:

- The data challenge: practical and legal impediments currently hinder the potential to use different types of data in prevention, which need to be addressed to increase precision in individuals, families, population groups, or neighborhoods at increased risk, combined with individual empowerment and health literacy.
- Trust, ethics, and community engagement: public health actions should focus on population-specific needs, policy development, and delivering effective and ethical interventions. Crucial activities include engaging communities, sharing data, building coalitions, improving health literacy, and developing a diverse educated workforce. A fundamental concern is whether precision technologies can exacerbate health disparities or create barriers to access for certain populations. Ethical principles of justice, fairness and equity in access will therefore need to guide assessment of precision technologies, in addition to various health technology assessments.
- Behavioral Science: personalised prevention assesses risk, which needs to be managed by the person exposed and stakeholders, including health workers, who can affect risk behavior

and exposure. This suggests a behavioral science research agenda to develop an evidence-based approach to tackling risk.

- Health Sector integration and beyond: as personalised prevention interventions develop, they need to be integrated into health services, raising questions about health worker capabilities, systems support, financing/reimbursement, and incentive mechanisms to support prevention interventions.
- Technological advances add new markers that may help better identify subgroups of individuals with different risks of having a disease, which eventually could improve prevention strategies at the individual level. Integrating markers of risk into scalable intervention packages is key to achieve population impact.
- Political economy of prevention: what gets recognized, becomes policy and implemented, is not just a question of the evidence at hand, but also of the political economy, a social science conceptualisation of what gets done or not. During PROPHET stakeholder consultation it became evident that a stakeholder forum for multisectoral coordination and advocacy was desirable, at regional as well as national level. Such a forum could work on the narrative and positioning for prevention, and approach policymakers and stakeholders across sectors.
- Inequities in health and personalised prevention: Inequities in health outcomes are driven by differential risk mostly linked to biological and socio-economic factors. Measures across promotion, prevention, and treatment need to be adapted and highly contextualized to improve health.
- Scaling up- Implementation Research: As interventions are put into practice in complex health systems, issues around implementation and operational questions need to be addressed.

In summary, to realize its potential the precision field needs to take a life course, multisectoral approach using different types of data also to prevent disease and not restrict itself to using omic information to treat established disease. This implies a far-reaching research and innovation need, new governance mechanisms, and a balanced agenda assessing both individual utility and public health implications at population level.

2.6.2 Stakeholder engagement strategy

This specific activity is ongoing and will be completed and validated within the project lifespan. The stakeholder engagement strategy is implemented through the PROPHET Platform and the PROPHET Forum. One of the foundational elements of the PROPHET project, and subsequently the development of the SRIA, is the continuous engagement of stakeholders in the realm of personalised prevention, following a process defined as co-creation. This collaborative approach aims to bring together researchers, policymakers, healthcare professionals, patient and citizen representatives and other key stakeholders to drive advancements in the field. To achieve this, a thorough stakeholder mapping exercise, based on the "snowball methodology", was conducted to identify and categorise relevant stakeholders across Europe. This process started by identifying key stakeholders, suggested by partners, then extending the process to other stakeholders who mighthave an interest in the project. A (confidential) database of contacts was then established, which is continuously updated with new data, ensuring a thorough follow-up and involvement of stakeholders from all relevant groups. Access to this database is limited to PROPHET project partners.

The stakeholder engagement strategy outlines the approach to engage experts from various sectors, ensuring that the potential stakeholders' concerns and needs are considered in the development of the SRIA (Table 2).

Diverse channels and tools have been used to reach stakeholders, informing them about project activities and results, and encouraging their active participation in knowledge sharing activities such as workshops. At the heart of this engagement process is **the PROPHET Forum**, a stakeholder community that gathers stakeholders from all relevant categories. The Forum is managed and coordinated by the PROPHET project team, **with regular outreach to stakeholders to engage them in project events and ask them to contribute to the SRIA co-development process**. To facilitate exchanges and interactions among Forum members, the **PROPHET Platform** was developed as a **community platform**. The Platform offers members the ability to set up individual profiles, use features such as unity web platform bilateral exchange through a matchmaking tool, share information with peers and with the PROPHET team, access event information and recordings, and engage with co-developed documents, including the SRIA and related documents. This coordinated approach, supported by the PROPHET Forum and Platform, aims to maintain a stakeholder engagement process that is crucial for the success of the PROPHET project and the development of the SRIA (Figure 5).

Figure 5. Stakeholder engagement process in the SRIA development.

Table 2. Anticipated k stakeholders concerns and potential impacts to be addressed in the development of the SRIA.

Stakeholders	Concerns	Potential impacts
Patients & citizens	They are the most important key stakeholders as they are the ultimate beneficiaries of more targeted prevention and treatments. They may be concerned about the cost of personalised preventive treatments, access to genetic testing, etc.	Improved patients' and citizens' quality of life by adapting prevention to individual characteristics (including genomics and environment / lifestyle aspects).
Healthcare professionals	Concerns about the cost and feasibility of implementing personalised preventive approaches in health systems as well as the training and education on these new approaches.	Informed and trained professionals, emphasising prevention over treatment; early detection of potential risks among their patients and thus early approach to treatment where necessary; less overload in hospitals thanks to prevention and early treatment.
Researchers	Funding of research and collaboration with other stakeholders to advance in personalised prevention research.	New collaboration opportunities through research programmes to advance in the field of personalised prevention.
Policy makers & public authorities	Need to make new regulations or improve the existing ones as well as ensuring the safety and effectiveness of personalised preventive approaches and treatments. Validity of approaches across the EU and transferability of results.	Reduced burden on the health and social security systems thanks to prevention and early treatment, reducing costs. EU-wide approach and transferability tested through dedicated use cases which are nurturing the SRIA.
Insurers	Reimbursement processes of personalised preventive approaches.	Demonstrate the cost effectiveness & value of personalised prevention approaches, alleviating the burden on insurers.
Life Science Companies	Regulatory barriers for developing personalised prevention approaches and long processes.	Provide guidelines for the development of future personalised prevention approaches and "citizens" engagement.

2.6.3 The Delphi survey

The Delphi consultation process within the PROPHET project serves as a structured and iterative method for gathering insights and building consensus among a wide range of stakeholders, as

previously outlined. . To develop the final version of the SRIA (scheduled for release in September 2025), information on the participants in the Delphi consultations will be provided with the initial draft of the SRIA, which will serve as a starting point for collecting their feedback.

The first step of this consultation will coincide with the presentation of the first version of the SRIA during the Stockholm workshop in 2024. The draft SRIA will be sent in advance to stakeholders to allow them time to read and prepare for in-depth discusions during the workshop. Stakeholders will be presented with thoughtfully crafted questions regarding the draft SRIA, encouraging them to identify any additional priorities and propose crucial actions needed to shape an effective strategy for personalised prevention. Representatives from various sectors and disciplines will engage in structured discussions, sharing their perspectives and reflections on the proposed topics.Based on the outcomes of the Stockholm workshop, additional experts may be invited to participate if deemed necessary based on the initial discussions.After the workshop, a set of follow-up questions will be sent via email to refine the suggestions and prioritize changes to the SRIA. Through feedback mechanisms, the Delphi consultations encourage contributions, fostering an environment where all voices are heard, ensuring that diverse perspectives are acknowledged and valued. The process will consist of two rounds of consultations, with an expected duration of approximately five months, before proceeding to the next step: a public consultation of the SRIA - open to any potentially interested person, beyond the experts in the previous consultations.

This iterative exchange aims to facilitate convergence towards a consensus, identifying common themes, priorities, and essential operational strategies to promote personalised prevention efforts.

2.6.4 Public Consultations

The public consultation on personalised prevention is a process designed to involve any interested individuals in providing feedback and input on the development of the SRIA. This process is crucial to ensure that the SRIA reflects shared needs and concerns, ultimately leading to a relevant and positive impact.

The PROPHET strategy for the public consultation of the first draft SRIA consists of several key steps. First, we will announce the consultation through various channels, including the PROPHET website and platform, newsletters, and press releases, providing clear instructions on how stakeholders can participate to maximize engagement. Next, the draft SRIA will be made available on a dedicated PROPHET webpage, with options to download the document. To gather feedback, we

will create an online survey containing specific questions related to different sections of the SRIA, using both open-ended and closed-ended questions to collect qualitative and quantitative input. Additionally, we will promote the draft SRIA at national and international events, encouraging discussions and gathering feedback during these sessions. Finally, stakeholders will be invited to submit their feedback directly via email or through the PROPHET Stakeholder Forum, ensuring that all input is incorporated to refine the final version of the SRIA.

3. The challenges of personalised prevention

Challenge 1: Continuous evidence synthesis system supporting personalised prevention

Status

In the past decades, numerous genetic, genomic, and more general 'omics' technologies have been developed, significantly enhancing the accuracy of diagnosing health conditions and providing new tools to predict disease onset and progression. Continuous evidence generation is crucial to support the implementation of personalised prevention approaches that adopt such technologies. Many studies have aimed to evaluate the ability of these tests to predict the presence or absence of specific genes, genetic variants or other biomarkers (analytical validity) and their accuracy in predicting future clinical outcomes (clinical validity). Although evidence on these dimensions, combined with safety data, may suffice to introduce a test to the market, demonstrating its clinical utility is essential for integration into personalised prevention strategies within national healthcare systems. As explained in par. 6.1, clinical utility, though not universally defined, generally refers to the test's usefulness (or value of the information) to provide actionable information that improve patient relevant health outcomes. While analytical and clinical validity provide foundational evidence for the potential of a test, clinical utility addresses the real-world effectiveness and impact of the test on individuals' outcomes (for instance, it is noteworthy to say that very commonly, the evidence on clinical validity of genetic tests are scanty across all the possible ancestries, that limit the transferability of evidence across populations). Demonstrating clinical utility involves proving the efficacy of the test in reducing the health burden of the condition for which it is used (clinical efficacy), as well as studying other dimensions crucial for its implementation. These include cost-effectiveness, acceptability of the test among clinicians and citizens/patients, organizational feasibility, and its impact on health inequalities. To date, although the evaluation of these dimensions is formally required within

structured evaluation frameworks, like Health Technology Assessment (HTA) or other assessment models (par. 6.1), there is a **significant lack of primary evidence** on both the **clinical efficacy** of these tests **and all other dimensions.**

Gaps

The gold standard for studying the clinical efficacy of these tests is the development of randomised controlled trials (RCTs), which are considered the highest level of evidence in the evidence pyramid, ranking just below systematic reviews and meta-analyses of RCTs[25]. In these trials, the personalised preventive intervention (or strategy) incorporating the use of genetic or genomic tests is compared with the standard of care to assess its efficacy in improving health outcomes. RCTs are highly valued for their ability to provide the most reliable evidence of clinical efficacy due to their rigorous methodological design, which includes randomization and controlled conditions to minimise bias. However, developing such study designs is challenging in the realm of genetic and genomic medicine due to the low prevalence of specific genetic conditions, the continuous development of promising technologies that might make a trial outdated before it is terminated, and the vast combinations of gene panels and interventions that need to be studied[26]. Moreover, limited sample sizes in trials and issues related to data sharing represent significant obstacles to achieving the statistical strength required to provide robust evidence on health outcomes. In primary and secondary prevention trials, these challenges are even more pronounced due to the substantial time lag between the implementation of the intervention and the observation of expected health outcomes, which complicates the measurement of long-term efficacy. Despite these challenges, generating solid evidence on the ability of preventive interventions that include genetic or genomics tests to reduce the health burden of these diseases remains crucial. Also, the studies on the impact of a test in terms of cost-effectiveness, patient acceptability, equity, and feasibility are likewise quite rare. One reason for this scarcity is that such evidence often necessitates prior proof of clinical efficacy, which is frequently absent or contentious. Without a solid foundation of clinical efficacy, it becomes challenging to justify and investigate these additional dimensions. Furthermore, the study of these impacts is sometimes context-specific, requiring research within the country where the test is intended to be implemented. Variations in healthcare systems, patient populations, and socio-economic conditions mean that findings from one context may not be directly applicable to another. Hence, there is a critical need for localised studies to ensure the technology's effectiveness and relevance in

the target setting. Moreover, while these domains are formally included in HTA, clear criteria for their evaluation are often lacking, leading to their underestimation in formulating recommendations These research gaps—including the scarcity of sufficiently robust studies on clinical efficacy and the limited evaluation of broader impacts—are equally pronounced across other omics sciences, where the evidence base is even more constrained. Indeed, the mapping activities conducted within this project (Annex) reveal a markedly lower volume of studies addressing clinical validity, clinical efficacy, and HTA reports in these fields compared to genetics and genomics, highlighting the need for further efforts to strengthen the evidence base in these areas.

Priorities and implementation

Strategies to study the clinical efficacy of personalised preventive approaches

Based on the considerations above on RCTs, it is essential for clinical and epidemiological expertise to assess the most suitable study design for each approach, considering both validity and feasibility. Different approaches are being developed to enhance evidence generation, particularly on genetic and genomic tests.

For example, while large-scale RCTs comparing test-based approaches with standard care are often challenging to implement, more focused RCTs can be designed to evaluate the efficacy of therapies or preventive interventions within specific risk categories identified by genetic tests. A classic example is the *BRCA1/2* test for women at risk for personalised breast and ovarian cancer prevention, recommended by major national and international guidelines. The high diagnostic accuracy of the test and the significant increase in incidence and mortality risk associated with the specific variants justified seeking the best possible evidence on the efficacy of various primary and secondary preventive interventions (such as prophylactic surgery or active surveillance) specifically in this high-risk population[27]. Other examples where RCTs have been implemented to study the efficacy of therapies on risk-stratified populations include the 21-Gene Expression Assay and the 70-Gene Signature for personalising breast cancer treatment. The multicenter MINDACT trial, initiated in 2007 across nine European countries, is an example of a non-inferiority RCT aimed at studying whether “high clinical risk, low genetic risk” patients have a non-inferior five-year survival without chemotherapy compared to with using it[28]. These targeted RCTs, while still requiring significant

sample sizes, long follow-up periods, and substantial costs, might represent a more practical approach than broad-based trials in the general population.

Specific considerations can also be made regarding the outcomes to be evaluated. While the final goal of any preventive intervention should be to reduce the incidence and/or mortality of a disease, intermediate endpoints can sometimes serve as effective measures for evaluating clinical efficacy. For example, the MyPeBS trial, designed to compare a personalised approach using a polygenic risk score (PRS) for breast cancer screening with the standard of care, focuses on an intermediate endpoint[29]. The trial's primary objective is to assess whether the personalised approach reduces the incidence of advanced breast cancer diagnoses. While intermediate endpoints, such as reductions in late-stage diagnoses, can be useful for evaluating preventive strategies, it is crucial to ensure that these endpoints reflect an impact on the ultimate outcome of interest, such as mortality, in the context of oncological screening programmes.

Some genetic and genomic tests have been developed to enhance the effectiveness of personalised prevention strategies that have already been studied. An example is the DNA stool test, which has been introduced as a more advanced alternative to the previously used faecal occult blood test for guiding individuals toward colonoscopy for early colorectal cancer detection[30]. However, while robust evidence of increased diagnostic accuracy in these trials has supported the recommendation of the DNA stool test, it is essential to conduct thorough assessments to ensure that the test's effectiveness applies to real-world clinical practice. This includes evaluating whether the test performs as expected in the target population and under routine clinical conditions.

Other strategies include the use of other methodological approaches, such as simulation models. For example, in 2021, a breast cancer simulation model developed by the Erasmus University Medical Center and the Georgetown University's Albert Einstein College of Medicine were used to evaluate the lifetime effects of different risk-tailored screening strategies[31]. A similar approach was already employed by the established Cancer Intervention and Surveillance Modeling Network to develop models that were used to inform the current USPSTF breast cancer screening guidelines[32]. These approaches generally allow direct comparisons between preventive strategies and can benefit from the use of data from biobanks or other real-world data sources. Employing these methodological approaches can enable the study of the impact of introducing genetic and genomic tests into prevention strategies. However, the evaluation of their validity and their use in generating

recommendations remains a highly debated topic. The validity of the generated estimates is contingent upon the quality of the data utilized and the robustness of the models developed. First, it is necessary to ensure transparency and reproducibility of the models; then, clear methods for assessing the model estimates are necessary. These methods should set standards for evaluating the credibility of the models, which are prone to bias since bias can arise from the input data and during the model calibration and validation phases[33].

Generating primary evidence on all the dimensions of clinical utility

To reduce the gap in evidence regarding the impact of the tests on various dimensions like cost-effectiveness, patient acceptability, equity, and feasibility, it is essential to invest in evidence generation in this field. Funding programmes should allocate resources not only to clinical efficacy studies but also to investigations focusing on these broader impacts. Certain dimensions of technology impact can be evaluated within the context of clinical trials designed to assess clinical efficacy. For example, incorporating patient-reported outcomes (PROs) into these trials can provide valuable insights into patient acceptability and quality of life. Similarly, assessing the experiences and feedback of clinicians during these studies can shed light on feasibility and practical implementation challenges.

Synthesise and evaluate evidence quality

In order to implement effective personalised prevention approaches, a priority should be to ensure that the evidence produced is synthesised and that clear criteria for evaluating the quality and robustness of evidence are applied. These criteria must evaluate the quality of evidence, including its validity, study design, and potential implementation levels. Based on the level of evidence, the output of the synthesis should be categorised according to different levels of strength.

To standardise and share it is necessary to invest in a system specifically designed to systematically synthesise evidence, ensuring that each piece of evidence is categorised based on its quality. This could be a dynamic, unified repository modelled on successful frameworks such as the U.S. CDC's Center for Precision Public Health, which utilises a tiered classification system for genomic medicine guidelines[34]. The system should allow for continuous updates as new evidence emerges, facilitating easy access to and retrieval of information.

Such a repository would serve as a valuable resource for healthcare professionals, policymakers, and researchers by providing a clear and structured overview of the evidence. This would support more informed decision-making and ultimately enhance the effectiveness and efficiency of preventive healthcare interventions.

Health Systems Integration

Health systems face numerous challenges when attempting to integrate and deliver personalised prevention approaches that are adapted to diverse local contexts. One of the primary obstacles is the creation of assessment tools that are tailored to the specific needs and structures of each healthcare system. The complexity of designing evaluation frameworks that account for local epidemiology, resources, and healthcare infrastructure means that a one-size-fits-all solution is rarely feasible. Moreover, the challenge of data sharing is significant, as the effectiveness of personalised prevention relies on access to large, diverse datasets to enhance the accuracy of evaluations and evidence generation. Ensuring interoperability between different health systems, while safeguarding patient privacy and data security, is a critical hurdle. This lack of unified data can slow the development of robust methodologies for assessing new omic technologies, ultimately hindering their adoption. Therefore, fostering collaboration across regions and countries, and developing standardised yet flexible frameworks, is essential for realising the potential of personalised prevention in different healthcare settings.

Considerations

As we advance the integration of genetic and genomic tests into personalised prevention strategies, several critical considerations must be addressed to ensure their success and sustainability. It is essential to recognise the rapid pace of technological advancements in genetics and genomics, necessitating continuous evidence synthesis efforts and regular updates to evaluation frameworks and assessment guidelines. This dynamic landscape requires a flexible approach to research and policy-making, ensuring that emerging evidence is swiftly incorporated into practice.

Investing in primary research by funding studies that are both feasible and effective in evaluating clinical efficacy is necessary. These studies should be designed considering the progressive steps needed for implementation from bench to public health practice. While expert matter knowledge is

necessary to ensure the accurate and comprehensive assessment of the intended outcomes, such implementation considerations are crucial to ensure that the studies are appropriately tailored to respond to the correct questions along the translational spectrum. Furthermore, additional primary studies are needed in the other omics sciences, which, while promising, still lack sufficient evidence, limiting their broader implementation and integration into clinical practice.

At the same time, it is important to establish clear parameters for evaluating this evidence. Creating standardised evaluation criteria will help ensure that the results of these studies are consistently and transparently assessed, facilitating their integration into healthcare decision-making processes. This combined approach of robust primary research and clear evaluative frameworks will support the effective implementation of personalised prevention strategies.

Challenge 2: The PROPHET Framework implementation

Status

Since the early 2000s, various frameworks have been developed to evaluate the clinical utility of genetic and genomic tests. Despite many efforts, there is still no widely accepted criteria for evaluating preventive approaches that use genetic and genomic technologies. This lack of standardised criteria has caused inconsistencies in how different countries and regions evaluate and implement these technologies. Moreover, the varied methodologies and evaluation criteria in different frameworks have led to a fragmented understanding of clinical utility, making it harder to make informed decisions about adopting genomic technologies in healthcare systems, especially in resource-limited settings.

In 2021, the European Union made significant progress by approving a new HTA regulation[35]. The regulation aims to encourage streamlining of the assessment process, allowing member states to evaluate jointly the clinical data and evidence submitted for a health technology. This aims to address the lack of consistent methodology and processes across EU Member States, which leads to considerable variation in the evaluation of vaccines, drugs, and medical devices. The new regulation, set to be fully implemented by January 2025, marks a crucial step towards more unified and consistent assessments of health technologies across Europe.

Gaps

Despite the progress made with the new HTA regulation, significant gaps remain in the evaluation of genetic and genomic tests. One major challenge is the lack of primary evidence that informs any assessment, which makes it difficult to obtain informed decisions about adopting and implementing these technologies. This issue is compounded by the absence of consensus on the dimensions and indicators that should be used for recommendations. Without agreed-upon criteria, standardising evaluations and ensuring all relevant aspects is tough[36].

Moreover, the HTA has traditionally focused on evaluating the clinical efficacy and cost-effectiveness of tests, often overlooking or undervaluing other potential impacts that implementing a genetic or genomic technology can have[37]. Although we agree that clinical efficacy is a *conditio sine qua non* to further assessing any test, we acknowledge that effective implementation of personalised preventive approaches requires a comprehensive evaluation that considers various factors, including feasibility, costs, allocative value, patient acceptability, the personal value of the test information, legitimacy, and equity. These dimensions are often context-specific and can vary significantly across different countries and populations.

Priorities and implementation

The PROPHET framework aims to address the aforementioned gaps by providing a holistic approach when evaluating and implementing personalised preventive approaches. This framework includes all relevant aspects - professionals, tools, technology, resources, clinical and community pathways - to ensure a thorough and comprehensive appraisal of these approaches. The goal is to guide public health authorities in adopting personalised preventive approaches using both health system and value-based perspectives.

The PROPHET framework builds on the HTA model promoted by the new European regulation, which mandates a joint assessment of the efficacy and safety of the technology at the European level and an evaluation of context-specific dimensions, such as economic aspects, feasibility, and acceptability at the national level (for further details please refer to Appendix 1, Section9.2). To comprehensively evaluate a personalised prevention approach, it is essential to ensure not only that the impact of the test on these dimensions is assessed, but also that these evaluations are conducted in collaboration with all stakeholder groups and are structurally considered when providing recommendations on implementation. The experience of using Health Impact Assessment (HIA) for

non-health related policies provides valuable insights for a more holistic and context-specific evaluation of personalised prevention approaches[38,39]. In the context of genetic and genomic tests, these policies relate to determining the reimbursability of such tests and establishing the pathways for these decisions within the health system. Additionally they may include requirements for mandatory testing prior to specific medical interventions for making a test mandatory before certain medical interventions can be undertaken, similar to the model used for abacavir (drug used for the treatment of AIDS, based on a genetic testing before treatment). This approach will therefore improve equity in access to genetic and genomic tests. The HIA model emphasises the importance of structured and meaningful engagement of stakeholders throughout the evaluation process. This includes healthcare professionals, patients, policymakers, and community representatives, whose perspectives and concerns are vital for a thorough assessment. By involving these stakeholders, the evaluation process can capture a wide range of impacts and ensure that the outcomes are relevant and acceptable to all parties involved.

Furthermore, the HIA model requires a comprehensive consideration of impacts, including factors that are often overlooked, such as health inequalities. This approach allows for a broader assessment that goes beyond the immediate clinical and economic impacts of the test to include its effects on different population groups and social determinants of health. For instance, understanding how a new genetic test might be perceived by different communities, its accessibility, and how it might exacerbate or mitigate health disparities is crucial for its successful implementation.

Additionally, HIA provides robust methodologies for developing programs that ensure the effective implementation and continuous monitoring of policies. This includes setting up systems for regular review and feedback, allowing for ongoing improvements based on new evidence and changing circumstances. The continuous monitoring aspect is particularly important as it helps identify any unintended consequences early on and provides opportunities to address them promptly.

In conclusion, the PROPHET Framework enhances the structured HTA evaluation implemented by the new European regulation with elements of HIA and a more structured monitoring plan. Implementing such comprehensive evaluations is undoubtedly complex and requires significant coordination and resources. Despite these challenges, our project has demonstrated that conducting these comprehensive evaluations is feasible within constrained budgets through three case studies in

different countries and examining different tests and related policies.[40] This approach ensures a more holistic and continuous evaluation of personalised prevention approaches.

Considerations

The development and implementation of the PROPHET framework should consider several critical factors:

- Regulatory Alignment: It is essential to align the evaluations with the new HTA regulation, focusing on centralised clinical data assessment while addressing national context-specific impacts. This alignment ensures consistency and reliability in the evaluation process.
- Stakeholder Engagement: Effective involvement of stakeholders in the evaluation process is crucial to ensure that all relevant impacts, particularly those related to inequalities, are considered. Stakeholders should be engaged in a structured manner to provide valuable insights and enhance the legitimacy of the evaluation process.
- Comprehensive Evaluation: The evaluation should use methodologies that incorporate both health system and value-based perspectives. This approach ensures a thorough assessment of personalised preventive approaches, considering all relevant dimensions and impacts.
- Policy Monitoring and Adaptation: Establishing programs for continuous monitoring and adaptation of policies is critical to ensure their effectiveness and relevance over time. These programs should include mechanisms for regular review and adjustment based on new evidence and changing contexts.

By addressing these considerations, the PROPHET framework can provide a robust and holistic approach to evaluating and implementing personalised preventive approaches.

Challenge 3: Data collection and integration, and Data Infrastructure

Status

A substantial increase in the creation of life sciences data has enhanced our understanding of disease risk, paving the way for preventative healthcare. To harness the potential of this data for personalised

preventative medicine, integrating life science data is essential, drawing from previous European experiences, and co-creating with other sectors. Lessons from the COVID-19 pandemic demonstrate the value of using unified frameworks and data-sharing structures. [41]. Research Infrastructures like ELIXIR, BBMRI, EATRIS, ECRIN, and EuroBioimaging have made progress, yet further efforts and investment are needed with a focus on three core areas: data quality and collection, data integration, and data infrastructure.

Healthcare-generated data, often clinical or ad-hoc, is typically not reusable. To overcome fragmented data collection it is crucial to identify and implement best practices using proven models as examples. Initiatives like Genomics England and disease registries (ERN-RND, The Danish Cancer Registry) aim to make clinical and genomic data accessible for research. Efforts in research and clinical-research settings have improved data management for access and reuse. Biobanks (e.g. The Estonian Biobank[42] and FinnGen[43]both part of the BBMRI-ERIC network) and repositories (e.g. the European Genome Phenome Archive (EGA)[44]) help support studies like Genome-Wide Association Studies (GWAS) investigating genetic disease components, aiding in polygenic risk score modelling for preventative approaches. However, it is not easy to extract actionable information immediately from omics data, as the complexity and variability of genomic data require significant curation, interpretation, and integration with other data types to yield meaningful insights.

The 1+MG initiative and the Genome of Europe project aim to unify national cohorts of genomic sequencing data, creating a key tool for understanding genetic disease drivers. However, fragmented, inaccessible, and inconsistent-quality data, especially from diverse sources such as socioeconomic, behavioral, and lifestyle data, present challenges for creating fully integrated, personalised preventive interventions[45]. Organisations such as GA4GH are working to cultivate a common framework of standards and harmonised approaches for effective and responsible sharing of genomic and related health data[46].

While substantial progress has been made, infrastructure and federated analysis tools at national and European levels remain insufficient for complex data integration—particularly with non-health data like behavioral and lifestyle variables, increasingly captured by personal devices, wearables, and lifestyle apps. These data types require distinct privacy, consent, and quality considerations, and their integration with health and genomic data demands robust data harmonisation and governance frameworks. Standardised platforms inspired by successful commercial models are urgently needed to help healthcare providers and researchers navigate and share data responsibly while respecting

patient consent. Frameworks like OMOP and HL7 FHIR are promising but require broader implementation, particularly as international and EU regulations evolve. With the exception of the BBMRI-ERIC Federated Platform, currently, national and European infrastructure and federated analysis tools are not advanced to deal with complex data integration and data coming from different sectors and sustained data infrastructure is limited. The European Health Data Space (EHDS), Genomic Data Infrastructure (GDI), and EUCAIM aim to integrate data and develop infrastructure that fits the necessary technical and ELSI requirements. Within GDI[47]15 countries have committed to establish a national node to manage human genomic data by 2026.

Gaps

Within the realm of healthcare data management, several significant gaps continue to pose challenges. One of the primary issues is the lack of standardization. The absence of widely accepted standards creates a fragmented ecosystem, which complicates the integration of data across different systems. It is necessary to consider how data from a wide range of biomarkers, including genomics, can be integrated and used to drive the development of personalised prevention interventions, and this fragmentation makes it difficult for researchers and healthcare providers to effectively work together and share information. The adoption of "minimal data sets" that distinguish "must-have" data from "nice-to-have" data is essential for guiding collection practices for both research and healthcare. To fully support prevention, consistent and longitudinal data collection needs to be supported, particularly from individuals when they are healthy, otherwise datasets will only address ongoing health challenges, rather than being useful to support prevention by flagging changes that may be indicative of the early development of disease. To address this issue, emerging standards like OMOP and HL7 FHIR hold great promise, yet they require broader implementation to truly make an impact, especially as new standards arise to accommodate multi-sectoral data integration. Another major hurdle is the challenge of data discoverability.The HDR-UK health data gateway is an example of an initiative to tackle many of these challenges[48]. Researchers often struggle to find relevant datasets due to the fragmentation of resources, poor data quality, and inconsistent data management practices. While the establishment of unified health and genomic records could significantly enhance discoverability, there are still many barriers to their effective implementation. Furthermore, the situation is made more complex when we consider the integration of data from sectors beyond healthcare, including socioeconomic and environmental data, which only adds to the challenge due

to variations in data structure, privacy concerns, and the contextual nature of these variables.

Accessing health and genomic data is critical for the advancement of personalised prevention and medicine. However, several obstacles continue to limit this access. Regulatory requirements can be daunting and create unnecessary hurdles, while the general lack of digital health literacy complicates the necessary administrative processes surrounding consent procedures and data-sharing policies. Additionally, the availability of high-quality data is often scarce, which underscores the need for clearer guidelines and practices that could facilitate better access.

Data reproducibility presents yet another challenge in this landscape. Gaps in quality assurance and the absence of comprehensive metadata can significantly impede research reproducibility, which in turn limits the applicability of research findings within clinical settings.

Moreover, effective data use mandates robust infrastructure and stringent security measures. For data to be integrated successfully into clinical environments, it must align with existing regulatory requirements, which is essential for safeguarding patient information.

Finally, translating research into clinical practice is not without its challenges. This process necessitates specialised training, fostering collaboration across various sectors, and ensuring alignment with regulatory processes. Additionally, it also requires the necessary tools and training for healthcare professionals to use whilst providing patient care. Addressing these multifaceted issues is crucial for unlocking the full potential of health and genomic data, ultimately enhancing patient care and outcomes.

Priorities and Implementation

- Standardisation: Implement standardised practices at both international and national level as recommended in the 1+MG Framework and supported by global and EU standards by GA4GH and ISO, for data structure and standardisation in health systems to overcome challenges arising from the use of unstructured formats and competing standards.
- Discoverability: Develop unified health and genomic records, as best practices, to enhance data discoverability at local, regional, national, and eventually international level. Efforts should focus on creating tools and platforms that facilitate easy and effective search and validation of appropriate datasets.
- Accessibility: Address variations in data accessibility across nations by establishing clearer and consistent regulations and consent mechanisms.

- Reproducibility: Ensure the availability of high-quality datasets with comprehensive metadata. Attention should be given to addressing metadata gaps for different types of health data to support research, regulatory purposes, and personalised prevention methods[49].
- Data Sharing: Establish secure approaches to data sharing, addressing reidentification and privacy concerns, ensuring patient and data safety at all times. Encourage organisations to adopt best practices for data sharing and enhanced digital health literacy to enhance collaborative efforts.
- Data integration: Ensuring that data integration adheres to FAIR (Findable, Accessible, Interoperable, Reusable) principles is crucial. This involves creating secure, standardised, and interoperable services under a common framework that respects jurisdictional boundaries for datasets while centralising and making metadata discoverable through common APIs. Multisectoral data integration: integrating socioeconomic and contextual data on e.g. environments need development.

Considerations

To realise preventive medicine, there is a need to systematically connect and access population, clinical, genomic, and lifestyle data to perform research at a larger scale. Due to the heterogeneity of clinical data, sustained curation and accessible research data are critical. The use of standards like Beacon V2 (being expanded to support DICOM queries) will facilitate the generation of virtual cohorts for linking data across different modalities. The utilisation of interoperable metadata models, data standards and semantic annotation will facilitate data analysis and training of AI models across different modalities of data and data sources.

To implement the infrastructure and data management required, capacity needs to be increased for the five functionalities of data management: data discovery, data reception, storage and interfaces, data access management, and processing. Additionally, infrastructure in the healthcare setting needs to be interoperable with the research domain, paying particular attention to cybersecurity and privacy. Capacity development in data discovery, reception, storage, access, and processing is necessary, particularly as AI/ML-driven prevention models become more prevalent. To support actionable insights, investment in clinician-friendly tools is vital so that providers can interpret validated models for personalised prevention.

Interdisciplinary cooperation is needed to set shared data standards, reduce bureaucratic obstacles,

and enhance healthcare efficiency.

Challenge 4: Responsible Research and Innovation:

Status

Current frameworks should be revised to proactively address ethical challenges associated with new advancements in personalised prevention[50]. Responsible research and innovation in this area requires a comprehensive approach that integrates ethical considerations into every stage of development. This includes safeguarding personal data and privacy but also fostering transparency in research and engaging with diverse stakeholders to understand and address their concerns. This approach will be needed to ensure that personalised prevention advancements are both innovative and socially responsible.

Gaps

The current model for effective test implementation overlooks the shared responsibility of public and private sectors in anticipating future challenges and their societal impact. Ethical dimensions, such as equity in access to these technologies, informed consent, and the potential for discrimination based on genetic information, are often underrepresented in traditional assessment frameworks. As personalised prevention becomes more widespread, there is an urgent need to evaluate not only the clinical and economic aspects of these technologies but also their broader societal implications.

Priorities and Implementation

- Reliable and valid instrument and process

The scientific merit of testing technologies in personalised prevention depends on incorporating standardised methods for quality control, clinical validity, and overall utility.[51] It is crucial to ensure that all testing technologies adhere to high standards.

- Focus on significant health problems

Responsible testing must consider factors such as disease prevalence, disease severity, financial constraints, and future implications to properly determine the appropriateness of certain tests over others.[52] [53]Though these considerations vary amongst individuals, the public and private sectors must

make thoughtful decisions to prioritise addressing the most important health problems and how to budget resources in proportion to other healthcare demands.[54]

- Benefit-risk ratio of advantages and inequities.

Similar to other healthcare initiatives, testing in personalised prevention should aim to maximise benefits while minimising potential disadvantages. Benefits may extend beyond clinical outcomes to include social and psychological impacts[47].

- Defining appropriate policies for the private sector

Stakeholders should assess the impact of current regulations on the private sector and consider whether additional policies, such as educational initiatives or transparent advertising, could improve responsible test implementation. To uphold autonomy, transparency, and trust, further regulations on the private sector are essential. These regulations should foster a responsible partnership and proactively address future challenges in personalised prevention approaches.

Considerations

Responsible test implementation is foundational for advancing responsible research and innovation. The outlined criteria emphasise the need for active stakeholder engagement to continuously monitor test implementation and address limitations that policies may not anticipate.[55]

Challenge 5: Community Engagement and trust

Status

Personalised medicine and prevention, in which genomic information plays an important role, envisions and requires active patients and citizens taking control of their health and care. They need to be well-informed to be empowered to make decisions that reflect their personal values, and be aware of options for data sharing.[56] However, what such engagement and empowerment entails may differ per domain relevant for personalised prevention: research, care or governance.

In research, patients with personal experience of a disease offer a unique perspective that, if explicitly incorporated, leads to science that is more relevant and translatable. Roles may range from “passive” study participants to “active” patients and the public being involved in all phases of research. In the

care domain, individuals should feel empowered to make health decisions regarding their health and prevention that align with their personal values and preferences, leading to more culturally sensitive and patient-centred care. The governance domain emphasises the involvement of the public and patients in decision-making processes regarding personalised prevention policies and programs, encompassing their participation in policy development, guideline formulation, and organisational governance structures.

For citizens and patients to become active partners in prevention, they must be systematically and meaningfully engaged in the planning, delivery and evaluation of these domains.[57,58] In recent years a range of instruments has been developed for engaging and empowering citizens and patients in various ways and to various degrees, ranging from one-directional methods, such as interviews to more collaborative participation in patient forums. Currently the former instruments are more frequently reported than the latter. The effectiveness and outcomes of engagement is often not measured.

Gaps

- Studies and reviews consistently report a lack of knowledge among citizens and patients regarding genetic information, while new concepts such as personalised medicine are not well-known. Lack of awareness and potential benefits may hinder acceptance and implementation of personalised prevention.
- Health care providers can help patients navigate genomic and personalised information, but often are also not sufficiently educated on these topics, and lack time for such additional tasks.
- Though elements of good engagement practices are more widely recognised (e.g. meaningful engagement needs iterative or continuous involvement, support and remuneration for patient input), evaluation towards specific goals for engagement is often lacking or patchy.
- Meaningful engagement requires dedicated funding and resources.
- Multisectoral governance poses a gap in community engagement as it requires effective coordination and communication between diverse sectors, such as healthcare, education, and policy-making, which often have different priorities and operating structures. This fragmentation can lead to inconsistent messaging, delayed decision-making, and challenges in aligning goals, ultimately hindering meaningful and cohesive community involvement.

Bridging this gap requires creating unified strategies that foster collaboration across sectors while ensuring that community voices are adequately represented.

Priorities and implementation:

- Concrete Involvement of Citizens and Patients: Actively engage citizens and patients through their organizations (NGOs and Patient Advocacy Groups) in personalised prevention policies, decision-making processes, and communication activities. This engagement is essential for addressing public concerns, fostering trust, and ensuring that prevention strategies are aligned with the needs of the community.
- Enhancing Community Engagement: Prioritise and improve community engagement, as defined by the WHO: "a process of developing relationships that enable stakeholders to work together to address health-related issues and promote well-being to achieve positive health impact and outcomes." This approach is fundamental to the successful implementation of personalised prevention strategies. [59]
- Education and raising awareness of options for personalised prevention and taking part in health research.
- Generate more structural funding for citizen and patient engagement in research, care and public health, and their governance.
- Develop and study online information and communication tools to disseminate knowledge on genetic testing and preventive options for citizens, patients, and their family members.

Considerations

- Currently more engagement practices focus on care and research by patients, rather than citizens. Citizens may be more difficult to reach and may need other information tools. Awareness of prevention may also be more prominent in school curricula.
- Online tools for information and communication may be difficult to access and understand for persons with low digital literacy and health literacy, potentially exacerbating health inequalities. More specific attention to inform and engage such persons may be needed, as well as to other individuals and communities that are marginalised or vulnerable and may have less access to or more distrust towards (health) institutions.

- Personal contact with health professionals may increase trust in personalised prevention and data sharing, however, this would not be a route for citizens.
  - Robust structures for responsible health data sharing data may boost trustworthiness (see also Objectives 3 on Infrastructure and 9 on ELSI)
- As research and care become more interconnected, good communication to patients and citizens is necessary to help them understand what they can and cannot expect from their contribution in regard to their own health and prevention.

Challenge 6: Health Professionals and Policy Makers involvement

Status

On an institutional, national and international scale, both health professionals and policymakers are essential in enabling the implementation of personalised preventive approaches in healthcare systems. Collaboration among stakeholders is critical to address regulatory, resource, and technological challenges. Policymakers should be encouraged to use stakeholder input and evidence-based research to guide their decisions. Ultimately, policymakers have the potential to help create and support robust infrastructures and responsible practices that foster significant change towards a future healthcare. Through engagement and cooperation, barriers to implementation can be overcome, resulting in a healthcare system that is more personalised, preventive, patient-centred and supported by the public.

Capacity building, education and information are important elements of engagement: well-informed policymakers are better equipped to draft and discuss policies regarding personalised prevention with other relevant stakeholders and sustain further responsible implementation across disciplines, domains and national borders.

A variety of policymakers should be distinguished because they have different roles and responsibilities regarding aspects of personalised prevention, and their educational needs may differ accordingly. Professional organisations of medical specialists decide on guidelines for implementation of specific tests, public health (screening) organisations may decide on e.g. stratification of screening programmes based on biomarkers, HTA organisations may decide on the

thresholds for added value used in the assessment, reimbursement experts may decide on economic aspects.

Increasingly education on genomics (as a tool in personalised prevention) focusses not only on genetic experts, but also on non-genetic health care professionals. The number of education initiatives targeting policy makers in public health programmes is limited. As a good example, USA cancer programmes (integrating a.o. BRCA testing) illustrate how state cancer genetics programs have partnered with cancer registries, clinical facilities, health-care providers, health systems, public and private payers, policymakers, other state, regional, and federal programs, academic institutions, community organisations, advocacy groups, and industry.[60]

Effective engagement with policymakers is crucial for the successful application of genomics in personalised prevention. Identifying relevant policymakers for specific applications is essential, as they influence research agendas, funding, guideline development, education, and the implementation of clinical innovations. Key components of this engagement include capacity building, education, and access to accurate information. Well-informed policymakers can better draft and discuss policies alongside stakeholders, promoting responsible and sustainable innovations across various sectors and borders. This process also necessitates addressing diverse and sometimes conflicting professional interests. Engaging stakeholders and fostering dialogue are vital for sound policymaking, enhancing public trust in data sharing, and supporting the ethical implementation of personalised prevention.

Gaps

- Economic models that demonstrate cost-effectiveness of personalised prevention are lacking. Education on HTA is thus needed.
- In assessing the evolving landscape of educational initiatives for non-genetic health professionals relevant for personalised prevention in healthcare, several gaps have surfaced:

  -Appropriate training is required for efficient stratification in public health screening.

  -There is a need for training in new categories such as somatic genomics related to the tumour.

  -Introduction of new methods of assessment of competences such as Entrustable Professional Activities (EPAs) will allow for a focus on applying knowledge and know-how in addition to know-what.

-Incorporation of public and patient involvement in education for health professionals.

Priorities and implementation

It is important to train healthcare professionals in personalised preventive strategies, culturally competent care, counselling, and use of data. An "enhanced" patient-doctor relationship is key to supporting behavioural change and ensuring patients have the information they need to make informed decisions about their health[61]. In the building phase following the development of the PROPHET framework, the PROPHET project will publish the Action Plans for the uptake of the PROPHET framework, fostering engagement and capacity building for health professionals and policy makers.

A toolbox for capacity building will be developed, including a range of materials for the various types of health professionals and policymakers . It will include factsheets, policy briefs, webinars, conference presentations. It is important to link to other initiatives and existing information materials and online tools also for non-genetic health professionals.[62]

In terms of the topics to be covered, the capacity building will need to include ethical and legal aspects related to big data and data infrastructures, evaluation of clinical utility including cost effectiveness, and disease pathways linked with prevention and treatment.

Consideration

To support personalised prevention in our European health and care systems, health care professionals and policymakers need to be engaged and therefore have specific training. Education can take the mode of face-to-face training sessions, but given the large number and variety of policymakers and health care professionals involved, online training modules and materials are increasingly more effective in disseminating knowledge. Further research is necessary to evaluate training modes and materials for specific purposes and target groups. It is to be expected that clinical geneticists will play an important part in being available for advice and coaching other professionals on more complex health problems.[63]

The fields of public health and genetics may be separated by different traditions and practices (e.g. regarding prevention, screening, and one-size-fits-all approaches), requiring time for alignment and integration.

Challenge 7: Regulatory aspects and synergy with private sector

Status

The implementation of prevention strategies requires synergy between public and private sectors. Public-private partnerships (PPP) are important for utilising the strengths and capabilities of businesses. These partnerships involve shared investments in research and development initiatives leveraging the strengths and resources of both sectors to address health challenges and create targeted measures.

Engaging with the private sector plays a role in advancing personalised prevention for various reasons:

- Innovation and Technological Advancements: Private firms, such as those specialising in biotechnology and health technology can lead the way in applying innovation. Their contributions as cutting-edge tools like wearable health devices and genomic technologies have great potential for prevention efforts.
- Data Handling: Successful personalised prevention initiatives heavily depend on data collection, integration and analysis. Private sector organisations possess the infrastructure and expertise for sophisticated data management including utilising artificial intelligence (AI) to extract valuable insights from health data. A comprehensive data strategy may include gathering and integrating various types of information, such as personal device data (e.g., physical activity, heart rate, and sleep metrics from wearables); environmental data (e.g., air quality, noise, and access to green spaces); school data on nutrition and mental health; technical diagnostic data like breast density and microbiome analysis; and lifestyle data (e.g., shopping habits, screen time, and school lunch consumption).
- Financial Support and Resources: Collaborating with companies can offer financial support and resources that go beyond public funding capabilities. This can expedite research and development processes facilitating market access, to preventive solutions.
- Execution: Involvement from businesses, historically and today, plays a role in expanding successful public projects into widespread healthcare solutions. Their expertise in

commercialising and distributing health technologies ensures that advancements in prevention can effectively reach various healthcare settings.

Gaps

Ensuring the privacy and security of health information is a concern, especially when private entities are involved. The development of data-driven healthcare tools necessitates collecting sensitive data, such as genetic, racial, and sexual orientation information, raising privacy, discrimination, and stigmatisation concerns. Additional data types, such as screen exposure and social interaction metrics (evaluating depth and frequency of social connections) also present challenges, especially regarding privacy. Furthermore, issues like inaccurate self-reporting and lack of standardised methods can introduce biases.64

- Including sensitive attributes can promote fairness by reflecting diverse populations, despite GDPR restrictions requiring strict safeguards like pseudonymization and consent.65 Balancing these regulatory constraints with the need for fairness through data inclusion is crucial for creating equitable and effective healthcare tools.
- Implementing data protection measures and establishing clear regulatory guidelines can help mitigate these risks. However, differences in standards across regions can challenge the smooth integration of new technologies. Aligning regulations and setting guidelines for prevention tools can promote better collaboration.

The secondary use of health data for personalised prevention faces significant regulatory challenges, including the fragmented application of GDPR rules across EU Member States which creates barriers for cross-border research.[66] The European Health Data Space (EHDS) proposal aims to harmonise the framework for primary and secondary use of health data, but raises concerns about individual control over data and the risk of bias if certain groups opt out.

Wearable devices like smartphones and smartwatches offer continuous, real-time health data crucial for developing personalised prevention tools, but their use raises regulatory concerns. Ensuring data validity,[67] and addressing the accessibility and privacy disparities associated with wearables, especially those producing continuous data, will require an aligned regulatory framework.[68]. Data from wearables must meet high-quality standards and protect user privacy.

With regard to the private sector and PPPs making genetic tests available to patients across Europe, a number of regulatory considerations need to be assessed. This includes whether the EU Regulation on In Vitro Diagnostic Medical Devices provides adequately high standards of safety and performance for genetic tests[69], and the impact of diverse legal requirements regarding medical supervision, genetic counselling and informed consent across European countries[70]. In addition, other potential regulatory initiatives, such as self-regulation of the industry and patient education need to be explored.

Priorities and Implementations

- Stakeholder Platforms: Establishing platforms where stakeholders from the public sector institutions and academia can collaborate on prevention strategies promotes knowledge exchange, joint ventures and coordinated efforts toward common objectives. Moreover, arranging workshops and conferences to promote cooperation and knowledge exchange between public and private sectors builds up PPP networks. Additionally, it is essential to establish trust between institutions and private companies. Being transparent in communicating and involving stakeholders in decision making processes can strengthen this trust and streamline cooperation. Establishing a culture of trust is paramount for patients and citizens to feel comfortable sharing their personal data, empowering them to become active participants in their own healthcare.
- Regulatory Sandboxes: These controlled environments allow for testing health technologies in various kinds of partnerships. This approach enables private companies to innovate while ensuring compliance with health regulations expediting the introduction of solutions to the market.
- Encouraging Private Sector Engagement: Implement detailed incentives such as tax benefits, funding opportunities or exclusive research collaborations to encourage private businesses to participate in personalised prevention plans. These incentives should be accompanied with strong privacy protections to ensure data security. This can lead to development of health-promoting solutions integrated with individual data, like wearable devices, personalised nutrition, genomic testing services, and Direct-to-Consumer (DTC) products. The public sector must set guidelines for responsible marketing and verify the scientific validity, efficacy, and clinical utility of these products, ensuring their availability and presentation as options rather than necessities.

- Framework for Evaluation: Provision of specific indicators for the assessment of the successes of PPPs in personalised prevention. Proposition of a regular evaluation process to ensure consistent improvements.
- Public Awareness and Education: Utilise media, awareness campaigns, public forums and other methods to educate the public on the benefits and potential of personalised prevention through PPPs.

Considerations

Collaborating with the private sector may be beneficial in many ways to advancing prevention efforts. By encouraging innovation, providing resources, and ensuring solutions private companies play a significant role in transforming preventive healthcare. Strategic partnerships, frameworks and a focus on ethical practices are vital for unlocking the full potential of this collaboration leading to more effective and personalised health outcomes. However, in dealing with PPP, the public sector should set up indicators for assessing the success of partnerships between public entities in personalised prevention enabling regular evaluation of their impact and efficacy.

Challenge 8: Access, Equity and Coverage

Status

To fully realise the benefits of personalised prevention and fulfill the promise of universal health coverage in European healthcare systems, equitable access is a key challenge. Access can be defined through the 5As[71]: availability, affordability, accessibility (including geographic barriers), adequacy (including quality), and appropriateness (whether the service meets the needs of different population groups). Governments and health stakeholders must integrate these dimensions into personalised prevention strategies for successful implementation. Key elements include reimbursement, coverage of interventions, and integration into basic healthcare entitlements and routine preventive care to ensure availability and affordability.

Other factors impacting access to personalised prevention include lifestyle and behavioural modifications, awareness and understanding of personalised prevention, knowledge of family medical history, and availability of genetic information to inform disease risk understanding. These elements relate to health literacy and patient/citizen empowerment.

Population-based prevention strategies often fail to meet the specific needs of vulnerable groups. Lower income and socio-economic status, often affecting minority groups, are linked to reduced access to health information and healthcare, leading to poorer health outcomes. Personalised approaches can help reduce health inequalities by addressing individual needs based on environmental, behavioural, socio-economic, and cultural factors. However, access and equity considerations must be integrated into implementation strategies from the very start.

Gaps

Insufficient focus on impact and investment in prevention: Low health literacy is often associated with limited awareness of the determinants of health, leading to less healthy behaviours, decreased participation in screenings and vaccinations, and healthcare avoidance. Increased investment in prevention, especially for vulnerable groups and health education, is essential. There is a need to move towards more integrated health services, based on a lifecourse approach and selection of services based on the holistic needs of a certain population.[72] However, budget constraints across European countries may hinder the provision and reimbursement of additional health services, despite the potential long-term savings and improved health outcomes from preventive measures.

Limited utilisation of digital health technologies: Digital transformation in healthcare requires significant investment and is still in its early stages in many European countries. Access to digital health technologies is limited, especially for vulnerable groups at risk of digital exclusion, such as older people, socially excluded groups, people living in areas with limited internet coverage, etc.[73] The use of AI in healthcare poses challenges regarding health inequities, as algorithmic models often include errors and biases due to continuous under-representation of many ancestry groups in health datasets. Efforts to improve digital health literacy across the population are needed to build trust and understanding of health data collection and sharing.

Lack of harmonisation across Europe: Varying approaches to health data privacy, genetic testing, and insurance coverage mean that patients and citizens across Europe do not enjoy the same rights. Healthcare systems' management and organisation remains the sole competence of EU member states, with varying health budgets and priorities. As a result, inequalities within and between European countries in access to health and social services remain. More harmonised approaches and increased solidarity among member states could help close this gap and foster more equitable access.

Priorities and implementation

A paradigm shift is needed to integrate personalised prevention into healthcare systems and achieve universal access to personalised prevention interventions. Three key priorities can help address the gaps outlined above: policymaking, collaboration and partnership among stakeholders, and outreach and training for communities and stakeholders. They overlap with priorities on community outreach/engagement (Objective 5) and capacity building (Objectives 5 and 6) which are elaborated above. Further complementary priorities for implementation are:

- *Policymaking:* Support the use of digital health technologies in healthcare while prioritising a regulatory environment which prevents discrimination and bias and safeguards citizens' control over their personal data. Health and social policies should be complemented by regulatory frameworks that protect against discrimination based on socio-economic status, health status, race and ethnicity, religion, gender identity and sexual orientation, etc.
- *Policymaking:* Integrate preventive approaches into health systems and routine clinical practice, such as regular health checkups for the general population and better preventive counselling, providing adequate access to underserved communities and minorities. This includes addressing geographic and cultural barriers to access to quality services, ensuring full coverage of relevant personalised preventive interventions by the national health insurance system, and earmarking funding for preventive health programmes, research, and infrastructure.
- *Collaboration and partnership:* Consider PPP with e.g. technology companies to develop and implement affordable digital health tools prioritising data security and privacy. Sustain the development and implementation of equitable personalised prevention interventions through diverse funding mechanisms and research programmes.
- *Outreach and training:* Prioritise awareness and health literacy programmes for the general public and patients about access to personalised prevention interventions. Specific efforts are needed to reach vulnerable populations through targeted/adapted messages and use of relevant media channels, including social media, television, radio, and community events.

Considerations

Integrating access and equity into implementation of personalised prevention is essential to building citizens and patients' trust, a notion that is addressed across other aspects of relevance to this project, from the development of data collection tools and infrastructure to responsible research and innovation. Providing citizens and patients with accessible, affordable, appropriate, and high-quality personalised preventive care will help realise the potential of personalised prevention for improved health outcomes. This requires sustained investment, supported by potentially new funding approaches and evidence on the medium and long term cost-effectiveness of personalised prevention interventions.

Challenge 9: Ethical, Legal, Social Issues (ELSI)

Status

Advancements in genomic sequencing, extensive health data, and digital integration in healthcare have enabled personalised prevention through tailored risk profiles that analyse genetic, behavioural, and socio-economic factors. As personalised prevention evolves, research into ethical, legal, and social implications will be crucial.[74] [75]Current efforts address privacy concerns by strengthening data protection and giving individuals control over their health information. As mentioned earlier in the text, emerging regulatory frameworks like the European Health Data Space will shape the processing of health data for both primary and secondary purposes[76].

Gaps

Collaborative research will be essential to integrate ethical, legal, and social principles into personalised prevention, ensuring innovations are accessible and contribute to a fair and equitable healthcare system.

Priorities and implementation

- Informed consent

Informed consent tools will be essential for ensuring citizens and patients understand the benefits, risks, and implications of personalised prevention strategies. These tools should provide clear,

accessible information about the nature of the tests, potential outcomes, and subsequent healthcare decisions while addressing privacy concerns and data security.

- Maintaining trust and deliver effective communication

To maintain public trust in personalised prevention, it is essential to implement safeguards against misuse (e.g. discrimination, etc.). Furthermore, effectively translating and communicating knowledge to all stakeholders will be crucial for realizing the full potential of personalised prevention.

- Building evidence

The implementation of new technologies and research findings faces significant challenges, including limited evidence of clinical utility, varying interpretations of benefits, institutional resistance, data integration issues, a need for improved clinician understanding and patient-centered ecosystems, etc. To successfully implement personalised prevention strategies and enhance healthcare outcomes, it is crucial to address these challenges, improve data sharing, and incorporate public perspectives.

- Ensuring data privacy

In personalised prevention, key concerns include ensuring privacy, maintaining database integrity, and regulating data sharing and data access for authorised users and allowed purposes. Standardising data formats, protecting against unauthorised access, and providing adequate storage and computational infrastructure are crucial for securely managing health information to advance prevention strategies effectively.

- Ensuring fair access

Ensuring fair access in personalised prevention requires equitable distribution of outcomes, balanced disclosure of sensitive attributes used to develop personalised prevention approaches, regulated commercial involvement, and fair distribution of potential benefits.

- Concerns regarding linking different sources of data

With increasing health data from personalised prevention, it is crucial to address the risks of cross-linking health information to derive new information about individuals. Robust guidelines are needed to ensure safety controls and protect sensitive patient information.

Considerations

To effectively integrate ELSI principles into practice, collaboration among researchers, healthcare providers, policymakers, industry leaders, and advocacy groups is crucial. Interdisciplinary research and dialogue can help develop comprehensive guidelines and frameworks that address these complex issues. This approach will enhance the ethical implementation of personalised prevention, build public trust, and ensure equitable access to advancements, ultimately promoting a fairer healthcare system.

Challenge 10: Changing behaviour

Status

For personalised prevention to reach its full potential citizens and patients need to be aware of preventive options, and know how to take actions towards interventions or behaviour change to actually achieve prevention or better health. Increasingly, we are better able to personalize risk prediction for certain disorders, e.g. based on genetic information, but our understanding of behaviour change, and personalizing options for such change is limited. Merely providing information is not enough to influence behaviour. People may not understand the information, they may not be interested or motivated to change their behaviour, or they may not feel confident or in control of their behaviour.

Social sciences, health sciences and behavioural sciences have focused on various aspects of interventions to change behaviour[77]. Nudging behaviours has been shown to be effective in promoting healthy behaviour for instance in changing diet and smoking cessation. Nudging techniques include improving accessibility, adapting presentation of information and providing financial or emotional incentives for behaviour. Much research has focused on how to present risk information combining written text and numerical presentation with visual presentations to publics with varying degrees of health and digital literacy.

Gaps

The discussion on promoting behaviour change in personalised prevention takes place across the domains of public health and clinical genetics, each with their own traditions. Whereas in public health behaviour is stimulated when the outcome is seen as to be in the best interest of all (e.g. exercise), in genetics the emphasis has been on making an informed choice requiring counselling. This is particularly important when genetic information on a familial disorder has consequences for reproduction or in the case of invasive interventions such as preventive surgeries for hereditary cancers. In practice also in public health it is important to ensure informed consent, for instance for participating in screening programmes. On the other hand, patient decisions regarding new applications of personalised prevention, such as pharmacogenomics and lifestyle-related advice based on genetic susceptibility may be more similar to traditional public health approaches. More research is needed on acceptability, ethics and effectiveness of information and health-related choices in these cases. This also pertains to the influence on motivation of the context of being offered a test or tool by the healthcare system versus buying a direct-to-consumer (genetic) test or health device[78]. Findings about consumers accessing e.g. cancer screening after receiving a test result may have been influenced by a prior interest in one's own health, underlying the purchase of such a test[79].

From the recent history of genetic testing we have learned that genetic information of the risk to develop a disorder or susceptibility is not per se effective. After identifying a monogenic subform of common disorders conveying a 50% risk of having inherited a pathogenic variant, such as BRCA-related breast cancer, hereditary colon cancer or cardiovascular disorders, about 40-50% of first-degree family members decide to have genetic testing themselves. Interventions have tried to increase uptake by a more pro-active role of health care professionals helping the patient to inform family members, while also digital tools for communicating information to family members have been introduced. Having an affected family member in these situations is nonetheless seen as an important incentive to seek out care. In the situation that less informative tests with lower risks are used for multifactorial disorders, without a family history, motivation for behaviour change or uptake of interventions may be low[80]. In recent years studies have been conducted on behaviour change after receiving polygenic risk scores that indicate a relatively modest risk for a variety of disorders,

suggesting some positive changes[81] in adapting lifestyle, medication or screening, without increasing anxiety.

Implementation and priorities

Communicating personal risk information, such as gained via genetic tests, has the potential to stimulate healthy behaviour. It is important to better understand motivation for behaviour change by developing standards for best practices in communication of genetic information and of measuring relevant outcomes for behaviour change, such as uptake of screening, changing lifestyle, anxiety, et cetera[82].

For interventions to be effective various levels should be addressed and connected: the individual level and choices made, the community level, taking account of the relevant (healthcare) context of the individual and their health needs and characteristics such as health literacy, and the societal level allowing for the accessibility of care and prevention via funding or regulation and public-private partnerships.

Consideration

In developing personalised prevention approaches, information and choice should be key cornerstones of promoting healthy behaviours, as behavioural interventions and encouragements should never be based on fear or force, and especially genetic risk information may be misunderstood. For instance a belief in genetic determinism may be connected to feelings of fatalism and reluctance to change behaviour, or overoptimism against changing lifestyle when perceived to be not at risk. The path forward aims to support citizens and patients in accessing and understanding information so they can make healthy choices themselves, as well as helps them sustain such behaviours..

4. List of abbreviations

Abbreviation, Acronym	Description
1+MG	1+Million Genomes
B1MG	Beyond 1 Million Genomes
CVD	Cardiovascular disease
DICOM	Digital Imaging and Communications in Medicine
DCT	Direct-to-consumer testing
EGA	European Genome Phenome Archive
EP PerMed	European Partnership for Personalised Medicine
GDI	Genomic Data Infrastructure
GoE	Genome of Europe
GWAS	Genome-Wide Association Studies
HIA	Health Impact Assessment
HTA	Health Technology Assessment
ICPerMed	International Consortium for Personalised Medicine
LEA	Essential Levels of Assistance
PDTA	Diagnostic Therapeutic Assistance Pathways
PPP	Public-private partnership
PRECeDI	PREvention of Chronic DIseases
PROPHET	A personalised Prevention Roadmap for the Future Healthcare
PROs	Patient-reported outcomes
PRS	Polygenic risk score
RCTs	Randomised controlled trials
SRIA	Strategic Research and Innovation Agenda
THCS	Transforming Health and Care Systems

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6. Annex 1

6.1 Mapping Results

The main results of the Mapping phase of the PROPHET project are organized around the following themes: Biomarkers and digital technologies for risk prediction; Clinical utility of genetic and genomic tests; Clinical utility of biomarkers for personalised disease prevention; State of the art of personalised prevention approaches and critical factors for the adoption by healthcare systems; Existing Research projects and programmes in the field of personalised Prevention; Data management and infrastructure requirements to bring research advances into Health Systems, outlining challenges and best practices; Current practices of citizens', patients', health professionals and policy makers engagement in personalised Prevention and their gaps/bottleneck.

A visual inspection of the mapping results can be found here:

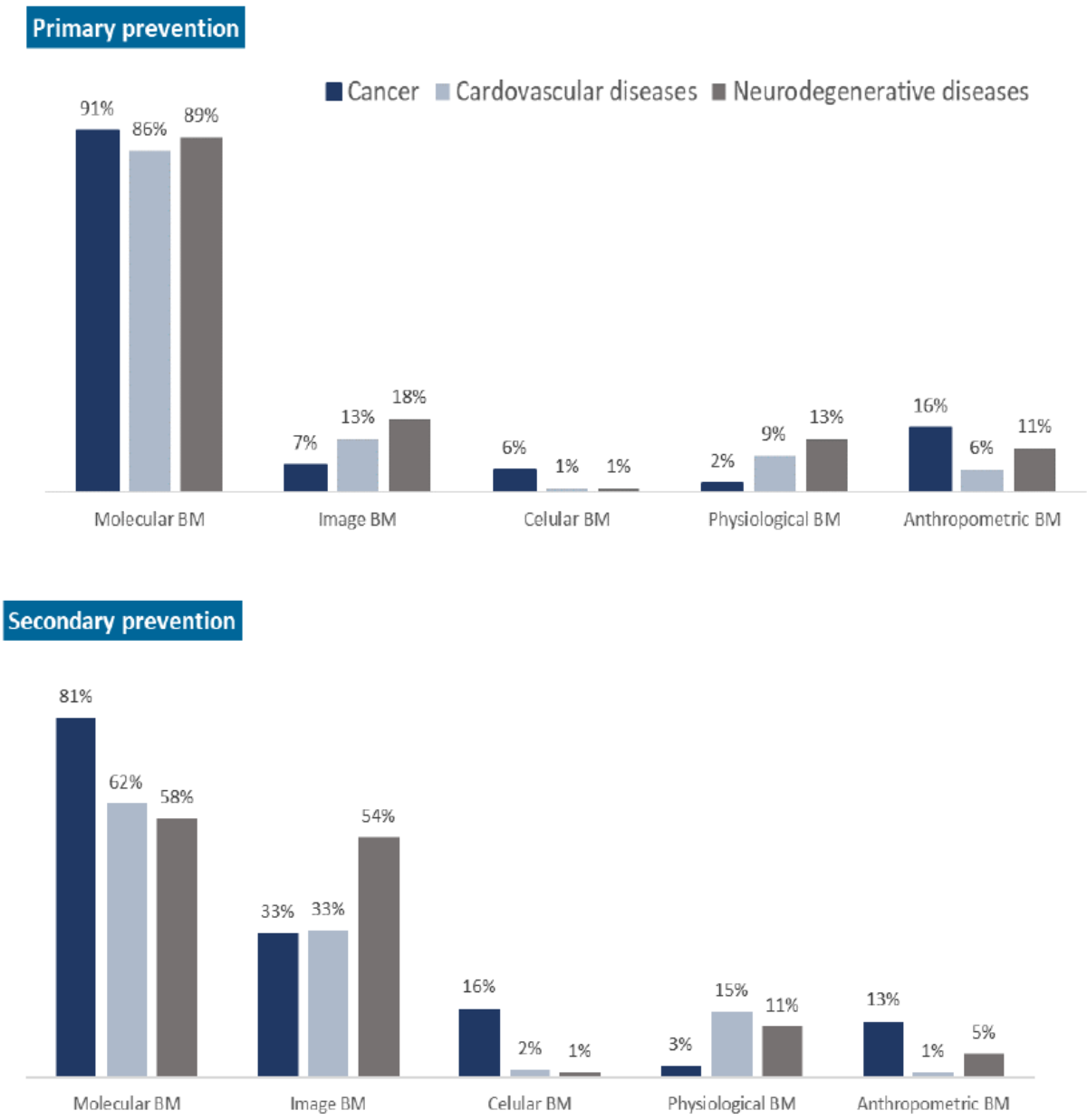
Below we summarize the most relevant results for each mapping activity within PROPHET.

Biomarkers and digital technologies for risk prediction

We systematically mapped and reviewed biomarker research in cancer, cardiovascular disease (CVD), and neurodegenerative diseases for personalised prevention in various settings. Results revealed a robust research landscape, particularly in cancer (843 articles) and CVD (775 articles), while fewer publications were identified for neurodegenerative diseases (286 articles), with a notable emphasis on Alzheimer's disease biomarker research. Molecular biomarkers predominated across all diseases, especially in cancer, while genetic/genomic biomarkers were prevalent in primary prevention, and biochemical biomarkers were common in secondary prevention across all conditions. Imaging biomarkers, particularly relevant in neurodegenerative diseases' secondary prevention, and digital technologies, notably AI and machine learning, were utilized primarily in molecular and

imaging studies. In conclusion, these rapid scoping reviews provided a comprehensive overview of the biomarker research landscape for primary and secondary prevention in cancer, CVD, and neurodegenerative diseases. Figure A1 summarizes the main results, and the details can be found in the academic manuscript. [83]

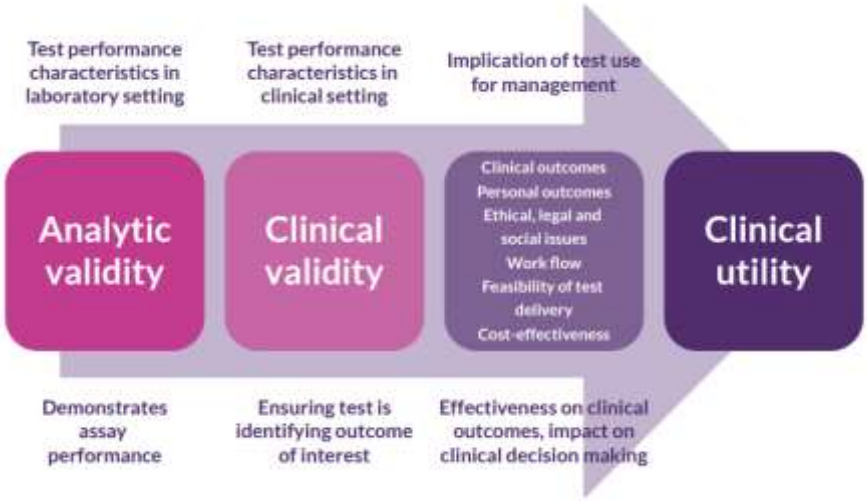
Figure A1. Overview of biomarkers in primary and secondary prevention mapped in PROPHET, according to the disease category.



Clinical utility of genetic and genomic tests

To align the consortium on some fundamental aspects of the project, the mapping activity began with a preliminary study of the concept of clinical utility and the dimensions to be evaluated. The term "clinical utility" does not have a singular or universally agreed-upon definition and, given its broad nature, it can be interpreted and applied in various ways. Generally, this term refers to the usefulness or value of a health-related practice or test, but the dimensions necessary to evaluate in order to establish this value are debated (Figure A2).

Figure A2. Overview of the processes that can ultimately lead to demonstration of clinical utility.



*courtesy from PHGF

To establish this we examined the available definitions and dimensions of clinical utility reported in a number of frameworks used for genetic test evaluation.[84] This work led to the identification of ten unique dimensions: (i) acceptability, (ii) analytical validity, (iii) clinical validity, (iv) context, (v) economic impact, (vi) equity, (vii) feasibility, (viii) clinical efficacy, (ix) legitimacy, and (x) personal value. The detailed definitions of these dimensions are reported in Table A1. Overall, all these frameworks included three overarching dimensions: the test's analytical validity, clinical validity, and clinical efficacy. Furthermore, almost all frameworks (96%) included some aspects of economic impact. However, only seven frameworks (25%) included the evaluation of the test's acceptability and personal utility. Contextual, equity, and legitimacy factors were included in the evaluation by 22 (82%), 15 (54%), and 15 (54%) frameworks, respectively.[85]

Table A1. Dimensions of clinical utility of genetic and genomic test.

Dimension	Definition identified in PROPHET
Acceptability	The test's conformity to the wishes, desires, and expectations of patients and their families.
Analytic validity	How accurately and reliably the test measures the genotype of interest.
Clinical validity	The ability to detect or predict the associated disorder.
Context	Description of the test use, including the genetic variability, target condition, availability of treatment options and recommendations.
Economic impact	Assessment of the cost and economic benefits of genetic testing.
Equity	The test's conformity to the principle of just and fair distribution of health.
Feasibility	Sustainability of the intervention and the capability to address potential barriers to using it.
Clinical efficacy	A measurable change in symptoms, overall health, ability to function, quality of life, or survival outcomes of patients.
Legitimacy	The conformity of a test to social preferences expressed in ethical, principles, values, norms, mores, laws, and regulations.
Personal value	The indirect health-related and other non-medical benefits to the individual of having the information.

Clinical utility of biomarkers for personalised disease prevention

In PROPHET we aimed to establish the level of evidence for clinical utility of biomarkers across cancer, CVD, and neurodegenerative diseases. Test definitions were established for each biomarker, and searches were conducted across relevant databases. Additionally, general searches for genetic testing and polygenic risk scores were performed for each disease group. In cancer, 115 tests using 62 unique biomarkers were identified. Evidence supporting clinical utility was found for 15 tests, primarily focusing on genetic biomarkers for familial cancers like prostate and colorectal cancers. For CVD, 58 tests using 32 unique biomarkers were defined, with eight demonstrating evidence of

clinical utility. These tests often revolved around longer-term risk prediction and involved incremental modifications to existing tests or multifactorial models. In neurodegenerative diseases, 32 tests using 25 unique biomarkers were identified, but evidence supporting clinical utility was limited to one test. The results expose significant evidence gaps between promising novel biomarkers in research and their translation into clinical care for prevention.

Only a small proportion of tests had available evidence about their clinical utility and in fewer the evidence for clinical utility was positive, and supported use of the test in a clinical context.

Few tests are being **examined** for their **clinical utility**, and even fewer have **clinical utility demonstrated** (Table A2).

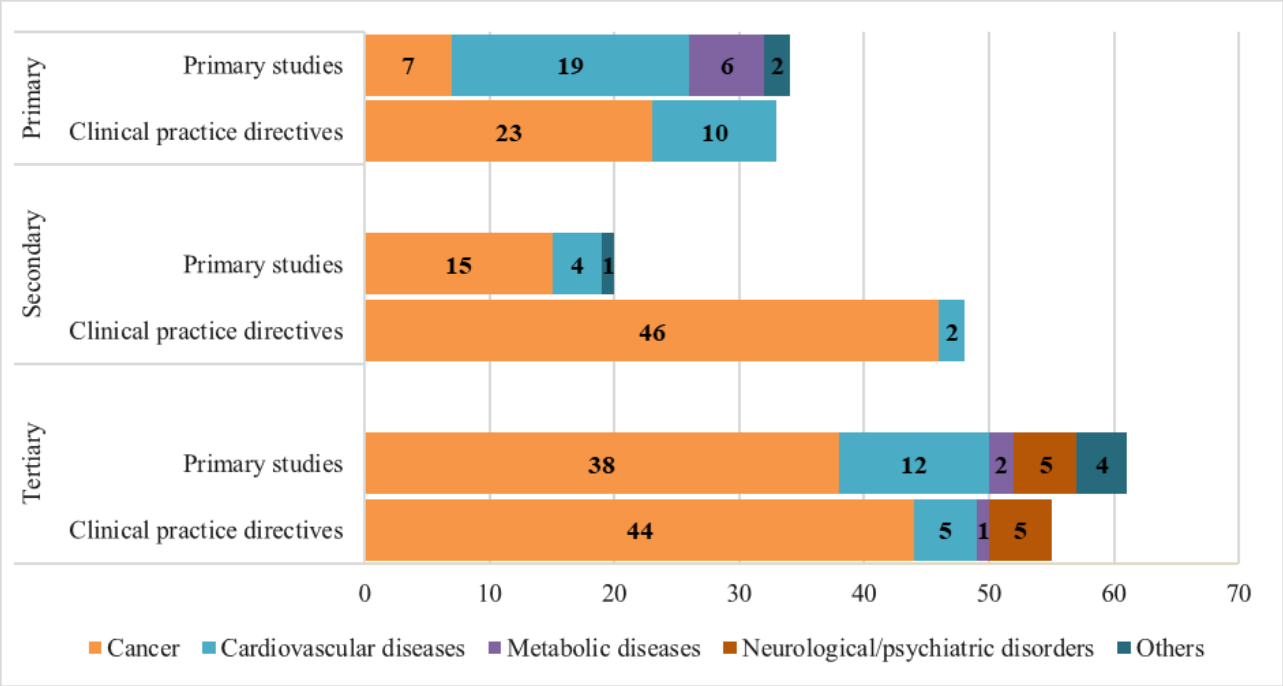
Table A2. Clinical utility of biomarkers from the mapping exercise according to disease categories.

	Cancer	CVD	Neuro
Unique biomarkers identified	62	33	25
Tests that **included identified biomarkers**	115	58	26
Tests with evidence **examining clinical utility**	22	8	1
Tests where the evidence **support clinical utility**	15	8	0

State of the art of personalised prevention approaches and critical factors for the adoption by healthcare systems

The aim of this mapping activity was to assess the state-of-the-art personalised Prevention approaches across Europe and identify the barriers and bottlenecks to their implementation in healthcare systems. A **Personalised Preventive Approach** is an action, or a set of actions, in which the information provided by **genetic and/or other omic biomarkers testing**, combined with demographic, environmental and behavioral characteristics, socio-economic and cultural context of individuals, **guides the decision-making** process regarding one or more interventions aimed at **preventing** the onset, progression and recurrence of diseases. A dual methodology was employed, combining a scoping review of the literature with stakeholder consultations. The scoping review included 120 records on personalised preventive approaches—comprising 60 guidelines, 60 primary studies, and 34 reviews on implementation barriers. From these records, 251 personalised preventive approaches were identified: 173 (69%) focused on cancer, 52 (21%) on cardiovascular diseases, and 26 (10%) on neurological, psychiatric, and metabolic diseases. Additionally, 67 (27%) addressed primary prevention using omic biomarkers, 68 (27%) secondary prevention with genomics for screening, and 116 (46%) tertiary prevention utilising pharmacogenomics or targeted therapies (Figure A3). The data reveals a notable imbalance favoring tertiary prevention of oncological diseases, prompting discussions on barriers to primary and secondary prevention for other chronic diseases and future project directions. Details can be found in the academic manuscript.[86]

Figure A3. Personalised prevention approaches mapped in PROPHET from the scoping review, according to the prevention levels and disease category, and classified by primary studies and clinical practice directives.



Analysis of the 34 studies on implementation barriers and bottlenecks highlighted issues such as lack of clinical utility evidence, guidelines, specialized professionals, citizen trust, and cultural concerns. These barriers affect national policies and the applicability of innovations across populations, risking increased health inequalities and discrimination. Most translational challenges (76%) were found in primary and secondary prevention of chronic diseases, particularly concerning non-European ancestry individuals (Table A3).

Table A3. Bottlenecks for the implementation of personalised prevention approaches from the scoping review.

mDOMAIN (%)	SUBDOMAIN	BOTTLENECKS (%)
Research (17)	Applicability across populations	33
	Lack of clinical efficacy evidence	27
	Lack of clinical validity evidence	26
	Lack of cost-effectiveness evidence	9
	Lack of analytical validity	4
Healthcare professionals (11)	Poor knowledge	80
	Limited acceptance	11
	Absence of specialized healthcare professionals	9
Public (25)	Psychological impact of results/communication concerns	26
	Discrimination/stigmatization	21
	Family	17
	Poor education	14
	Lack of trust and belief in personal benefit	13
	Willingness to be engaged in research	9
ELSI (13)	Data and privacy	54
	Social disparities	41
	Inequalities between countries	5
Economic issues (12)	High technologies costs	89
	Lack of reimbursement mechanisms	8
	Lack of resources	2
Implementation (22)	Operations and logistics	87
	Lack of guidelines	11
	Poor policy-makers knowledge	1

Furthermore, a **multi-stakeholder consultation** was conducted in two phases and included semi-structured interviews with experts and an online survey. Interviews to different stakeholder categories (namely Policy makers, Researchers, Health professionals, and Patient representatives). The data collected from these interviews were subjected to thematic analysis, which enabled the identification of key themes and issues related to personalised prevention to inform the survey design, complemented with findings from the literature on personalised prevention and healthcare innovation. This analysis ensured that the survey captured the most important insights from the expert discussions.

A total of 26 semi-structured interviews systematized in five levels highlighted the main barrier themes that were further explored in a survey completed by 270 participants, including stakeholder groups, healthcare professionals, citizens and patients, decision makers and researchers (Table 6). Overall, the main barriers reported were related to Health strategy, Awareness, education and literacy, and Ethical, Legal and social implications. Namely, main highlighted challenges were: a) Health systems strategies are geared towards curative care and not prevention; b) Awareness and understanding of the concept of personalised preventive interventions is low; c) There is a lack of basic and life-long training for health professionals on personalised prevention interventions; d) There is insufficient evidence for personalised preventive interventions to raise the necessary policymakers' interest; e) Health literacy of citizens and patients is low; f) There is insufficient evidence of cost-efficiency and regulation procedures for translation into health practice.

Identified barriers are interconnected, and the challenges extend beyond prevention to all personalised medicine interventions. Collaborative efforts are needed to elevate visibility and engage stakeholders, facilitating integration of personalised preventive interventions into healthcare systems for their widespread adoption. The many national, European and global initiatives currently ongoing (for instance ICPerMed, the 1+MG Initiative and countless national programs for genomic or personalised medicine across the globe) indicate an emerging opportunity to tackle the identified challenges. This momentum provides a platform for fostering dialogue among different end-users and stakeholders, facilitating the formulation of comprehensive and sustainable solutions aimed at resolving these challenges and overcoming persistent barriers.

Table A4. Main barriers for the adoption of personalised preventive strategies according to the thematic analysis of experts interviews.

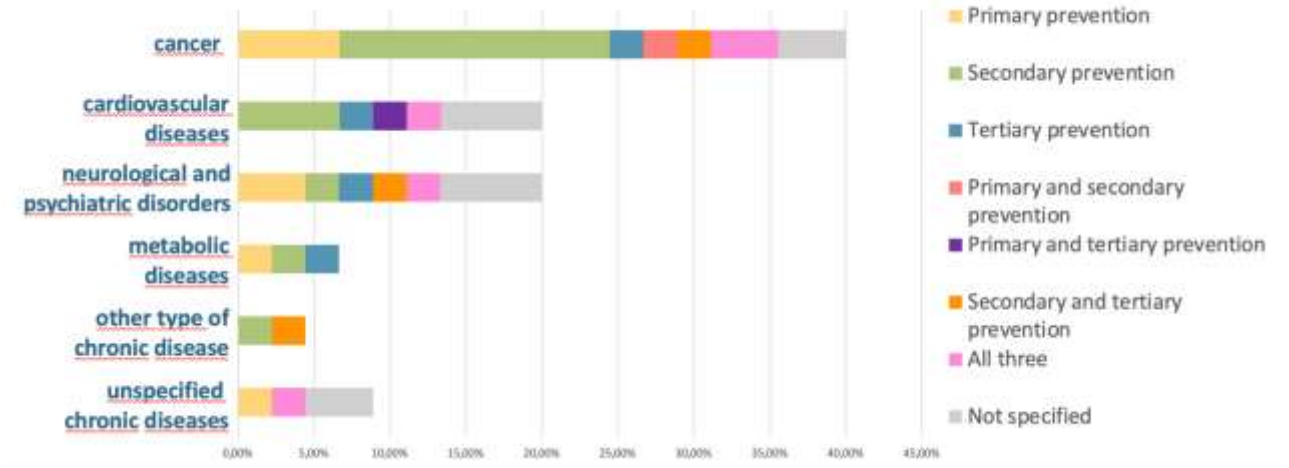
Level	Theme(s)	Sub-theme(s)
Healthcare system	Health strategy	•Focus on disease treatment not prevention •Lack of strategy for personalised prevention •Insufficient investment •Inadequate economic models
	Inequities in access	•Equity asymmetries
	Clinical practice	•Fractured patient doctor relationship •Clinical organization •Lack of standards
Research	Scientific strategy	•Insufficient research on prevention •Lack of standards on prevention research
	Scientific funding	•Insufficient funding streams
Implementation	Translational gaps	•Lack of regulatory frameworks •Length of time and costs of translation •Complexity of personalised prevention operationalization
	Synergies between healthcare, research and industry	•Collaboration resistance
	ELSI	•Lack of data governance and reporting regulation •Data protection issues
Awareness, education and literacy	Decision-makers	•Lack of awareness and literacy •Low political interest
	Health professionals	•Low awareness and insufficient knowledge •Insufficient training
	Citizens and patients	•Low health literacy level and knowledge •Low awareness •Misinformation/disinformation
Personal attitudes	Health professionals	•Resistance to change
	Citizens and patients	•Stigma •Fear And Discomfort •Lack Of Motivation

Existing Research Projects and Programmes in the field of Personalised Prevention

The primary objective of this activity was to map the current state of research on personalised Prevention in Europe. Definitions for key concepts such as “research funding programme” and “research project” were first refined and validated among the consortium members, basing on these assumptions the mapping activity was structured on a two-phase methodology: desk research and expert consultations. The mapping analyzed 1434 records, with 65 meeting the inclusion criteria, highlighting 5 principal funding programmes (2 European and 3 non-European), and 45 research projects funded by the European Commission. The European Commission allocated significant funds for personalised prevention research: 40% on cancer, 20% on cardiovascular diseases, and 20% on neurological and psychiatric disorders, followed by metabolic diseases and other chronic conditions. Approximately €160 million was allocated for personalised cancer prevention, nearly double the amount for cardiovascular and neurological/psychiatric disorders. The report emphasizes the prominence of cancer prevention, with Horizon Europe as a key funding programme aligned with the Mission Cancer.

In addition, most funded projects focus on personalised primary and secondary prevention (Figure A4). This strategic direction is particularly significant because it addresses the current lack of approaches in these areas (e.g., genetic testing to identify individuals at high risk for breast cancer), underscoring a research trajectory aimed at filling this critical gap. By prioritizing these areas, the funded projects indicate a focused effort to innovate and improve the precision and effectiveness of preventive approaches.

Figure A4. Distribution of funded research projects by prevention level and disease types.



Data management and infrastructure requirements to bring research advances into Health Systems, outlining challenges and best practices

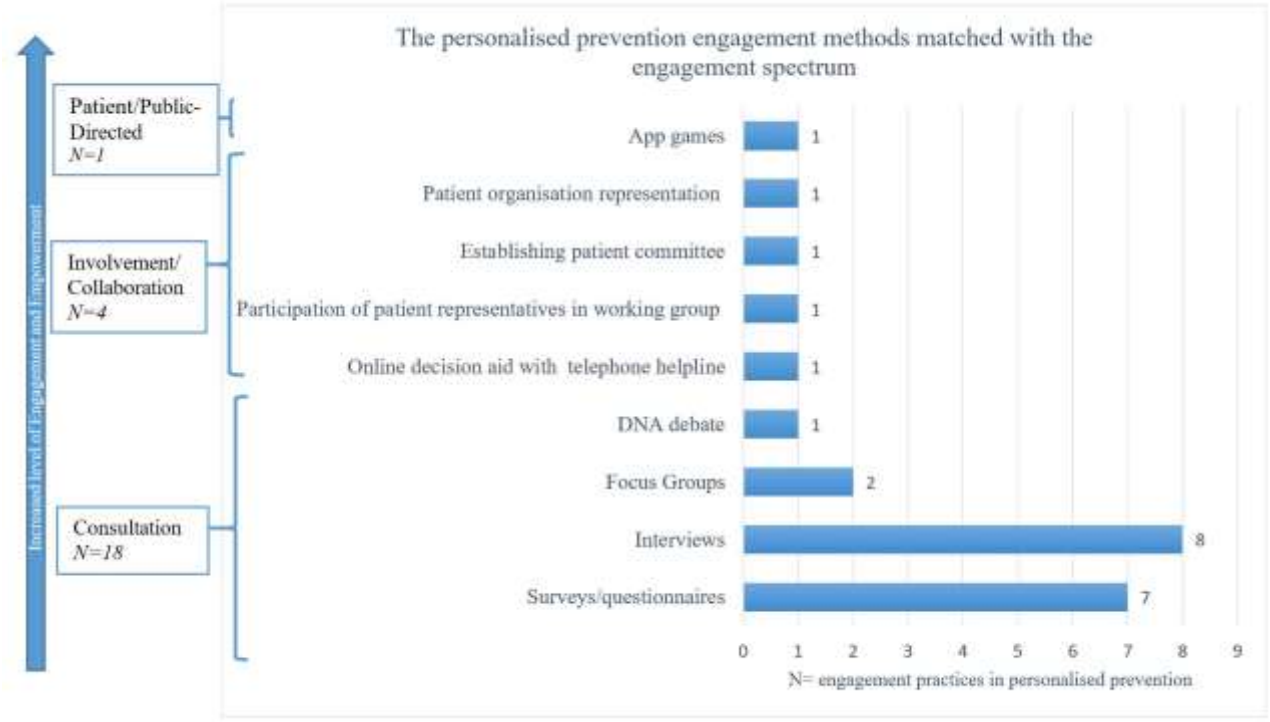
This mapping activity focused on identifying and addressing gaps and bottlenecks in data management and infrastructure, as well as highlighting a few best practices that impact cross-border health and genomic data sharing within European health systems. Semi-structured interviews with stakeholders and a subsequent thematic analysis were employed. Ethical considerations were strongly highlighted, including robust informed consent procedures, pseudonymisation of data, and ensuring multi-stakeholder engagement throughout the process. Stakeholders consulted were selected to ensure relevance, comprehensive coverage of key categories, and representation across different nations. Following the interviews, a workshop was conducted to integrate the responses obtained. Several challenges in data management were identified, such as the lack of standardization, issues with discoverability, variable accessibility, and difficulties with data reproducibility. Infrastructure-related challenges included data storage, processing, security, and sustainability. Implementation challenges involved integrating technical infrastructure into clinical settings, addressing workforce issues, navigating regulatory frameworks, and managing funding stream divisions. Furthermore, ethical, legal, and societal considerations underscored the variability in GDPR interpretation, legislative mandates, and the necessity for nuanced ethical frameworks. The broader ecosystem theme highlighted the need for cultural shifts, overcoming conservative attitudes, and addressing challenges in promoting data-driven solutions (Figure A5).

Figure A5. EU and national/regional infrastructures for data management.

Current practices of citizens', patients', health professionals and policy makers engagement in personalised Prevention and their gaps/bottleneck

The objective of this activity was to map engagement practices of citizens and patients and evaluate the scope and types of engagement methods employed in the field of personalised Prevention for common chronic conditions. By conducting a scoping review, literature from 2015 to 2023 was examined, utilising databases such as Medline, Embase, Scopus, Web of Science, APA PsycINFO, and IBSS. The focus was on practices involving patient and public engagement in personalised Prevention and genomics within the European context, specifically addressing cancer, cardiovascular diseases, and neurodegenerative disorders. The results encompassed 23 articles describing 23 engagement practices, revealing a spectrum of engagement levels. Predominant methods were one-directional, primarily involving dissemination and consultation such as through the use of surveys and interviews. Notably, engagement activities were predominantly associated with cancer (18; 78%), while none were identified for neurodegenerative diseases. Engagement practices vary according to relevant domains: *care* emerged as the most extensively explored area (14; 61%), followed by *research (2; 9%)*, a *combination of research and care (6;26%)*, and *governance paired with education (1; 4%)*. Results are summarised in Figure A6[87]

Figure A6. Results of the mapping of patients and citizens engagement methods in personalised Prevention in PROPHET.



A narrative review also addressed the training provided to non-genetics medical professionals, which has been developed over the past decade. This has partially aligned with the mainstreaming of genetic practices, enabling non-genetic specialists to order certain DNA tests within their areas of expertise and offer preliminary genetic counseling. The traditional competencies held by clinical geneticists—such as assessing, identifying, managing, and supporting individuals with inherited genetic disorders—remain essential but are now becoming relevant to a broader range of medical professionals. The rise of personalised medicine has also prompted the need to integrate genomics knowledge into public health initiatives, particularly in prevention and screening programs. Personalised prevention requires additional skills, including those necessary for risk-stratified prevention based on genetic profiles. New areas of genomics, such as somatic genomics related to tumors, have emerged, highlighting the need for targeted training. Medical education has adapted to these demands by incorporating competencies in so-called “entrustable professional activities.” Furthermore, involving patients and the public in the development of competency frameworks is increasingly recognized as crucial to achieving the goals of personalised medicine and prevention.

In terms of policymakers' engagement, it is important to identify which policymakers are relevant for specific applications of genomics in personalised prevention. Different policymakers play a role in

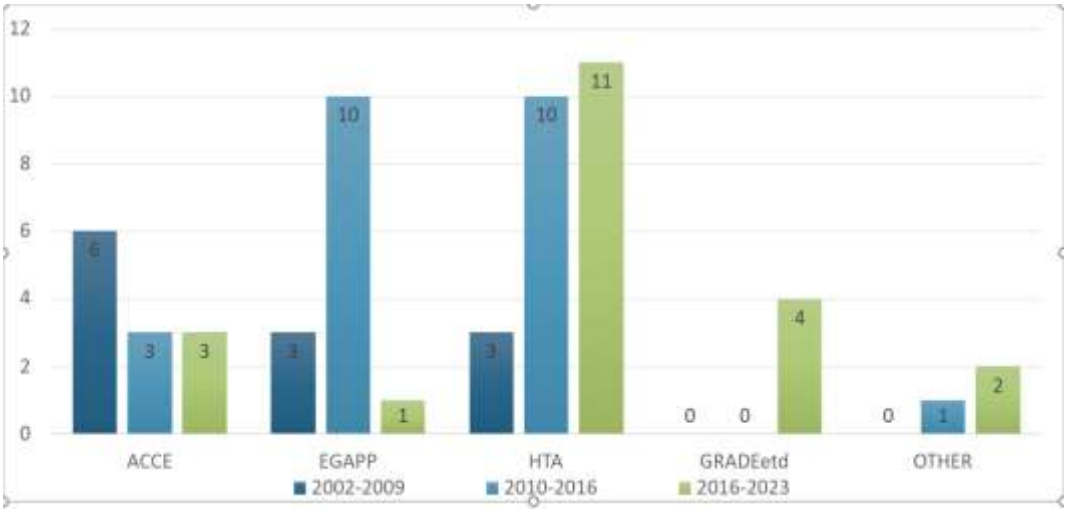
various aspects, such as setting research agendas, funding research, developing guidelines, shaping education, implementing innovations in clinical and public health screening programs, and evaluating outcomes, economic factors, funding, and reimbursement strategies. Capacity building, education, and access to accurate information are critical components of policymaker engagement. Well-informed policymakers are better positioned to draft and discuss policies related to personalised prevention with other relevant stakeholders, ensuring the responsible and sustainable implementation of these innovations across disciplines, domains, and national borders. This process inevitably requires addressing varying and sometimes conflicting professional interests and perspectives. Stakeholder engagement and dialogue are key to ensuring sound policymaking, fostering public trust in data sharing, and supporting the responsible implementation of personalised prevention.

Indicators for the evaluation of the clinical utility of genetic or genomic testing: a scoping review

This activity aimed to examine the dimensions and specific indicators measured in published assessment reports aiming at measuring the clinical utility of genetic or genomic tests. Formal assessments of genetic and genomic tests used for prevention were selected through PubMed, Web of Science, Scopus, websites of 20 different organisations, Google, and Google Scholar. Additionally, ten comprehensive dimensions of clinical utility were identified through an analysis of 30 theoretical frameworks for genetic and genomic tests**.** Indicators were extracted from the included assessments and clustered based on the comprehensive dimensions. From 3054 unique references and 12,000 grey literature search results, 57 assessments were collected. The assessment methods were Health Technology Assessment (HTA) (42%), EGAPP (25%), ACCE (21%), and other (12%) (Fig. 8). A total of 951 disease-specific indicators and 156 general indicators were extracted from the assessments. Analytic validity (60%), clinical validity (79%), clinical efficacy (79%), and economic impact (58%) were the most common dimensions, each having at least one indicator. However, only 12 assessments (21%) included indicators that compared health outcomes between tested and untested groups. Dimensions such as equity, acceptability, legitimacy, and personal value were evaluated in less than 15% of the documents. Details can be found in the academic publication. The study illustrates that, although dimensions such as equity and acceptability are significantly emphasised in traditional evaluation frameworks, they are often not considered in the assessments. Additionally, the study has underscored a significant dearth of primary evidence concerning the clinical efficacy of these technologies. The catalogue of indicators developed in this study serves as a valuable resource

for researchers, technology developers, and decision-makers, guiding research efforts to generate the necessary evidence for implementing these tests. It also forms the foundation for the PROPHET framework (Figure A7).

Figure A7. Formal assessments methodologies used for omics technologies mapped in the scoping review.



Mapping the ELSI challenges and bottlenecks in Personalised Prevention in Europe and beyond, including data protection (GDPR) issues in processing and linking genomic data, health/clinical data and other diverse data sources for Personalised Prevention.

The task explored the challenges and bottlenecks in the development of data-driven tools in personalised prevention, focusing on processing sensitive data like genetics, secondary use of health data, and integrating wearables. The findings revealed that while these tools can enhance personalised prevention efforts, concerns persist around data privacy, interoperability, and equitable access. The report highlighted gaps in EU regulations, especially regarding fair data use and compliance with GDPR. It concluded that greater collaboration between stakeholders and more targeted regulatory updates are needed to ensure these tools are implemented effectively and fairly across healthcare systems.

Mapping the current policy approaches with regard to direct-to-consumer personal preventive offers, especially Direct-to-Consumer (DTC) companies working in the field .

This task aimed to summarize the policies/regulations proposed or implemented to assess DTC-GT before it enters the market. Regulating DTC-GT in Europe is complex due to the wide range of DTC-GT services and the overlap of both EU and national laws. Studies show that European countries use different approaches to regulate genetic testing, focusing on areas like medical supervision, genetic counseling, and informed consent. While some laws may partially cover DTC-GT, there is currently no specific EU or national legislation for it.

6.2 The PROPHET Framework and the case studies

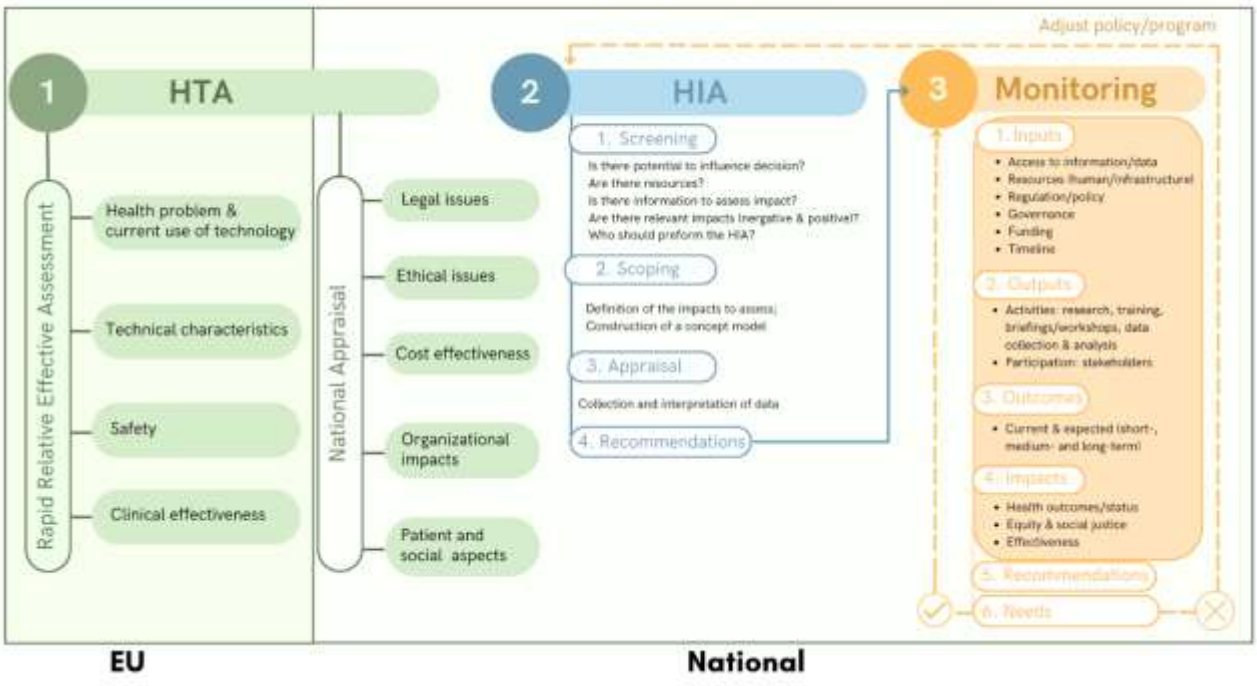
One of the principal outcomes of the PROPHET project is the development of the PROPHET Framework, which was created using a strong multidisciplinary approach. The construction of the Framework began with the results from the review on indicators for evaluating the clinical utility of genetic or genomic testing. The selected indicators were then incorporated into the clinical utility assessment model based on the HTA framework, in accordance with European Regulation (EU) 2021/2282.

Ideally, an HTA should be complemented by the national or regional prospective assessment of the impact of a prevention program or policy using that technology by Health Impact Assessment (HIA), in a process shared with relevant stakeholders (Fig. A8). By definition HIA assesses potential health effects of a policy through the consultation of a comprehensive group of stakeholders, supporting the decision-making process relative to the establishment of this policy (usually beyond healthcare), mitigating possible unconsidered impacts of the policies before implementation, for instance access inequities, and identifying indicators for monitoring the policy after implementation. Once implemented, the policy should be monitored, and any necessary changes should be proposed and re-evaluated through HIA.

The composed Framework was subsequently tested in three specific case studies to assess its applicability and to highlight potential strengths and weaknesses. The identified cases for testing the PROPHET Framework are:

- National policy that makes it mandatory to perform the *DPYD* genetic test before prescribing fluoropyrimidines to patients with colorectal cancer, carried out in three countries, namely Portugal, Finland and Italy;
- Introduction of the *BRCA* genes screening test into the LEA (Essential Levels of Assistance) to ensure its national reimbursement, and into regional PDTA (Diagnostic Therapeutic Assistance Pathways) for high-risk women (defined according to Italian AIOM guidelines).
- Introduction of a new national prevention program based on the use of the pharmacogenomic passport (U-PGx) across the entire population.

Figure A8. Overall PROPHET framework for genetic testing, including HTA complemented by HIA and a monitoring phase.



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