D1.3 Concept paper on Strategic Research and Innovation Agenda (SRIA)

Karolinska Institutet (KI) Leader, All Partners Contributors*

Co-Funded by the European Union

Table of contents

Contents

Table of Abbreviations and Acronyms

Abbreviation, Acronym	Description
ACCE	Analytic Validity, Clinical Validity, Clinical Utility, Ethical legal and social issues
B1MG	Beyond 1 Million Genome
BM	Biomarker
BMI	Body Mass Index
CVD	Cardiovascular Disease
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
ELSI	Ethical, Legal and Social Issues
EPPerMed	European Partnership for Personalized Medicine
ESFRI	European Strategy Forum on Research Infrastructures
EtD	Evidence to Decision
EU	European Union
GDI	Genomic Data Infrastructure
GDPR	General Data Protection Regulation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessments
ICPerMed	International Consortium for Personalized Medicine
IHD	Ischemic heart disease
NCD	Non-communicable disease
PH	Precision Health
PM	Precision Medicine
PP	Personalized Prevention
PPH	Precision Prevention Health
SDG	Sustainable Development Goal
SRIA	Strategic Research and Innovation Agenda
WHO	World Health Organization
WP	Work Package

Co-Funded by the European Union

List of Figures

Introduction

Advances in science and technology hold great promise and hope for new, improved ways to address global health challenges and ensure healthier populations worldwide. Currently non-communicable diseases (NCDs), also known as chronic diseases, are the world's leading cause of health burden and mortality. Globally, NCDs are responsible for 80% of the disease burden which will continue to grow given the aging population and are the main cause of death (74% of all deaths).[1,2] In a typical year, 17 million people worldwide die prematurely (before reaching the age of 70) from a variety of long-term health conditions, many of which are avoidable. More specifically, in Europe, these conditions account for 80% of overall deaths, representing the leading cause of avoidable premature deaths.[1,2]

NCDs are intrinsically linked to multiple risk factors, some of which are in principle modifiable including the behaviorome (e.g., lifestyle factors covering personal choices of diet, physical activity, smoking, alcohol, other substance abuse, etc), and the exposome (i.e. the spectrum of different parameters of living environments e.g. air, water, noise and light pollution), while others (e.g., age, sex, genetic predisposition) are not modifiable, but can be taken into account while assessing the individual risks in a longitudinal manner.
The majority of NCDs are preventable or can be delayed through interventions across the lifespan on the modifiable risk factors.[3] As part of the UN Agenda 2030, leaders of governments and states committed to develop ambitious national responses to reduce premature morbidity and mortality from NCDs by one third by 2030 through treatment and prevention (Sustainable Development Goals -SDG target 3.4).[1] Unfortunately, most countries are falling behind on the pace and their commitments to the SDG target.[4]
Population-level policies including those related to healthcare, infrastructures, and environment, are fundamental for NCD prevention; however they are not sufficient or as impactful as they could be . Individual-level prevention based on primary interventions including vaccination to prevent certain types of cancer, lifestyle education, and targeted secondary prevention such as screening for early-stage cancers, are also key factors that contribute to achieving the best possible population health status. Lastly, tertiary prevention interventions, including rehabilitation programs and any possible treatment of patients after disease onset that aims to reduce the burden of disability, are key to achieving the goal.

It has been stated that 80% of NCD could be prevented by changing modifiable factors.[5] Given the potential for effective preventive efforts in postponing the onset of disease, improving quality of life and reducing healthcare costs, the " precision-revolution" based on the use of emerging technologies and scientific innovations, with the exploitation of large volume of data from different sources, needs to extend to prevention.
By taking advantage of the improvement in understanding individual biomarkers, behavior and socio-economic risk profiles, and combining these types of information with individual lifestyle and environmental level interventions, this revolution aims to realize prevention strategies leading to both longer healthy life and potential cost savings.

Personalized Prevention: vision and aim

Personalized prevention (PP) revolves around the concept that the adoption of actions targeted to individuals in a population according to their risk might achieve better health outcomes compared to the traditional approaches. In 2022 during the kickoff meeting of "a PeRsOnalized Prevention roadmap for the future HEalThcare" (PROPHET) project, we defined PP as follows: "*Personalized 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 behavioral 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 ".* [6] Other terms used are Precision Prevention or Precision (Public) Health (PH or PPH). Yet, a wide range of interpretations of these terms (PM, PP, PH, PPH) has been reported in the literature. [7,8]

The technical development of high-throughput sequencing technologies, the digital revolution in healthcare, and the parallel development of targeted therapies in the last decade have enabled a transition from traditional medicine to personalized medicine (PM), but such transition in prevention of NCDs has been quite limited so far.

In 2019, the Personalized PREvention of Chronic DIseases (PRECeDI) consortium published some recommendations on how to integrate PM into NCD prevention.[9] While high-quality evidence continues to accumulate regarding the efficiency and effectiveness of PP interventions, we need to ensure that this progress is accompanied by concurrent changes in healthcare systems. These should include not only the reorganization of health services, but it should include also citizen engagement, education of health care professionals, and consideration of the broader social, legal and ethical aspects.

This is where the PROPHET project will contribute, by developing a Strategic Research and Innovation Agenda (SRIA) for PP in order to support the implementation of innovative, sustainable and effective personalized programs to prevent common chronic diseases. Our aim for the SRIA is to release a clear implementation path that all EU Member States can follow when introducing evidence based effective and efficient PP intervention for the benefit of population health and better functioning health care. To fulfill this promise, we need to approach PP by taking into account contributions deriving from previous and current initiatives in the field and scale them up in an integrated approach for primary, secondary and tertiary prevention across three levels: biomarkers, individual behavior, and environment/societal factors, and let the approach be influenced by relevant stakeholders by identifying and closing the knowledge gaps to implement personalized prevention at scale (Figure 1. Personalized Prevention approach in the PROPHET project).

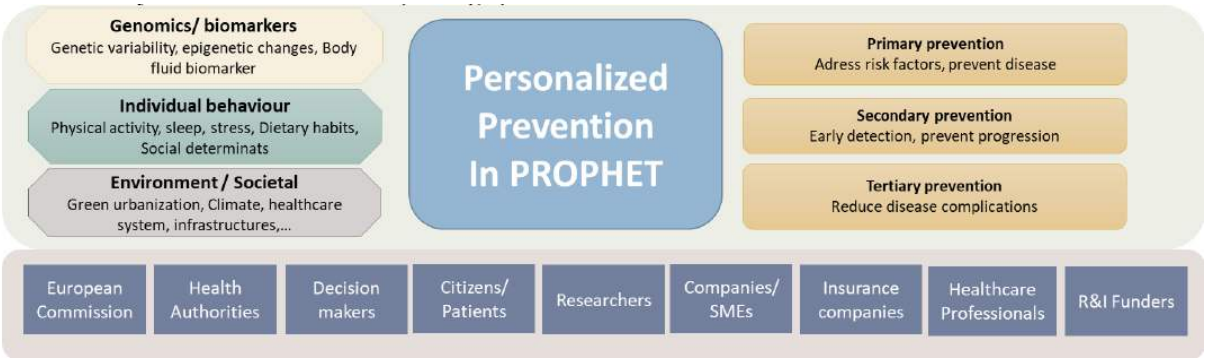

Figure 1. Personalized Prevention approach in the PROPHET project

There is a need to elucidate concepts and methods to integrate traditional preventive public health approaches with PM approaches that harness new technologies, combine biomarker data with individuals' behavioral and societal/environmental data to increase precision, effectiveness and efficiency of health promotion and preventive actions at different scales, including population-wide.[10] These personalized approaches will not replace existing traditional preventive health services but in some circumstance may improve the current system by integrating data sources and disciplines in order to target individuals based on their individuals' risk across the lifetime

While PM hitherto largely focuses on the individual, preventive efforts can be applied at the individual as well as at the societal level. Such strategies require a shift in which the broader health system, beyond health care, needs to be engaged, and individual risk should be addressed in a community context, especially for primary prevention in healthy populations with increased risk for disease. Still, careful consideration needs to be taken on potentially unintended harm of sophisticated PP actions: i.e. exacerbating social inequalities or exposing sensitive data.[11,12]

High impact essential NCD interventions can be delivered through a primary health care approach to strengthen early detection and timely treatment. Low-cost solutions exist for governments and other stakeholders to reduce the common modifiable risk in factors, named by the WHO as "Best Buys".[13] One key characteristic of these approaches to prevention is that they go beyond the traditional health sector and health system, towards building systems for health, across sectors and actors.[14] A preventive approach thus includes identifying individuals, families and groups at risk, and changing structures, activities, settings, and processes as well as the relationships between these factors with the final goal to improve the health in the community.[3] However, there is limited research about the use of system science affecting the macro-, meso- and microenvironments in public health.[15]

What's the Strategy?

Financial pressures before and after the COVID-19 pandemic weakened the sustainability of health systems in Europe. The European Group on Sustainable Healthcare stated that sustainable healthcare requires a shift from treatment of established diseases, to prevention of diseases and early diagnosis.[16] As such, the broader health ecosystem, beyond health care, needs to be engaged, and individual risk should be addressed in a community context, especially for primary prevention in healthy individuals.

The premise of precision in prevention is to predict and (successfully) intervene on risk at scale, in individuals as well as groups of individuals sharing similar or different characteristics. Here the high-risk compared to the population approach needs to be balanced recognizing Rose's prevention paradox, which states that a large number of people need to be included in a prevention program in order to achieve an effect in a minority of them.[17] 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 with effective interventions.[18] This is likely to vary across risk factors and diseases, and across different socioeconomic groups.

Central to this are data, of which we distinguish three levels in PROPHET (biomarker, individual behavior, environmental/contextual). There are also stages across the disease-, and life-course from healthy, "at risk" to sick, and corresponding actions across the promotion/primary prevention, secondary prevention, and tertiary prevention/treatment action levels, shown in ig.2

Regarding the definition of the prevention level, according to specific biomarkers, this seemingly straightforward classification often proves challenging to apply in practice, especially for primary and secondary prevention. Specifically, the use of biomarkers or predictive models to differentiate or stratify groups of individuals based on their risk of developing a disease can be useful for enhancing both preventive strategies (primary prevention) and tailoring early detection protocols (secondary prevention).

For this reason, in the PROPHET context, the level of prevention is determined by the preventive intervention that follows the predictive biomarker, as outlined below and in fig.3:

- *Personalized primary prevention*: primary prevention entails a comprehensive set of measures, strategies, or interventions aimed at proactively averting the onset of diseases before they occur and manifest. These initiatives focus on reducing disease incidence and mitigating risk factors through education, promoting a health-conscious lifestyle, and providing preventive medical treatments. The personalization of primary prevention is defined by the listed interventions, such as lifestyle adjustments, that are tailored to individuals who exhibit predispositions for a certain condition, considering the individual characteristics. In the case of genetic or other testing for primary prevention, they can be applied to all the individuals regardless of any background risk, as well as to individuals belonging to certain high-risk categories, such as specific age groups, as well as through cascade screening. The latter refers to testing healthy relatives of affected individuals with identified genetic variants, allowing for the identification of potential disease predispositions that may develop over the course of their lives and prevent their onset;
- *Personalized secondary prevention*: secondary prevention involves implementing measures to detect and treat existing diseases or health conditions at an early stage in

asymptomatic individuals that belong to traditional high- risk categories, with the aim of minimizing their impact and preventing future complications; in this scenario, personalization is achieved by utilizing biomarker testing and individual information to further stratify high-risk individuals. This identification can guide the implementation of in-depth diagnostic assessments, enabling early and effective disease detection. Furthermore, personalized secondary prevention, as well as primary prevention approaches, can leverage cascade screening, involving the relatives of individuals with specific characteristics. This enables the identification of heightened risks or conditions through predictive or diagnostic tests, ultimately guiding at-risk individuals towards more tailored screening programs.

- *Personalized tertiary prevention*: tertiary prevention refers to interventions and measures aimed at reducing progression and recurrence of a chronic condition, in order to enhance the quality of life for individuals dealing with such health challenges. In this context, personalization is facilitated through various biomarker testing modalities, including pharmacogenomics, employed on the affected patient. This comprehensive approach anticipates predispositions to potential complications, forecasts the individual responses to therapies, and prevents adverse drug reactions by adjusting the dosage and using the most appropriate medication, all with the goal of averting the worsening of the individual's condition.

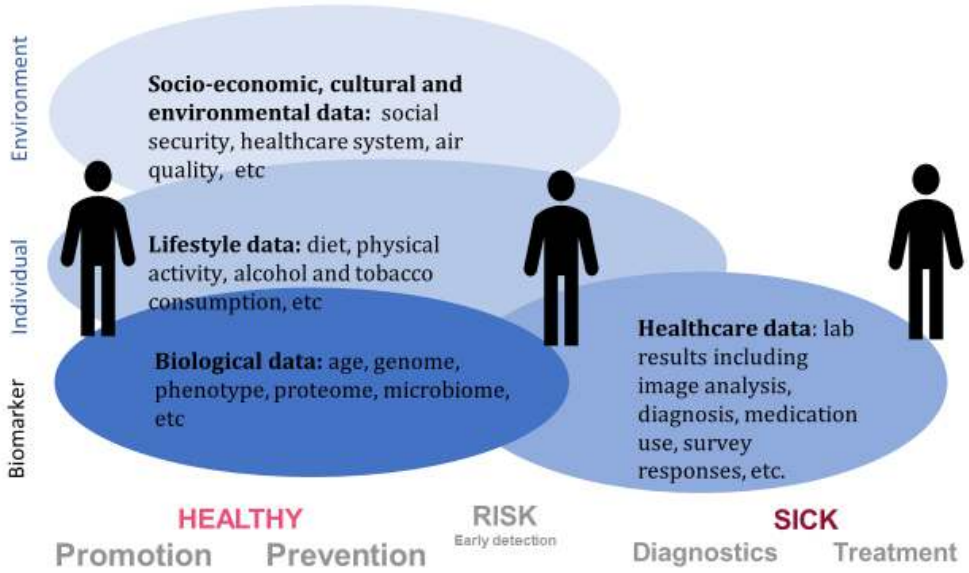

Figure 2. Potential source of information needed to achieve precision and personalization of prevention and treatment across the life course.

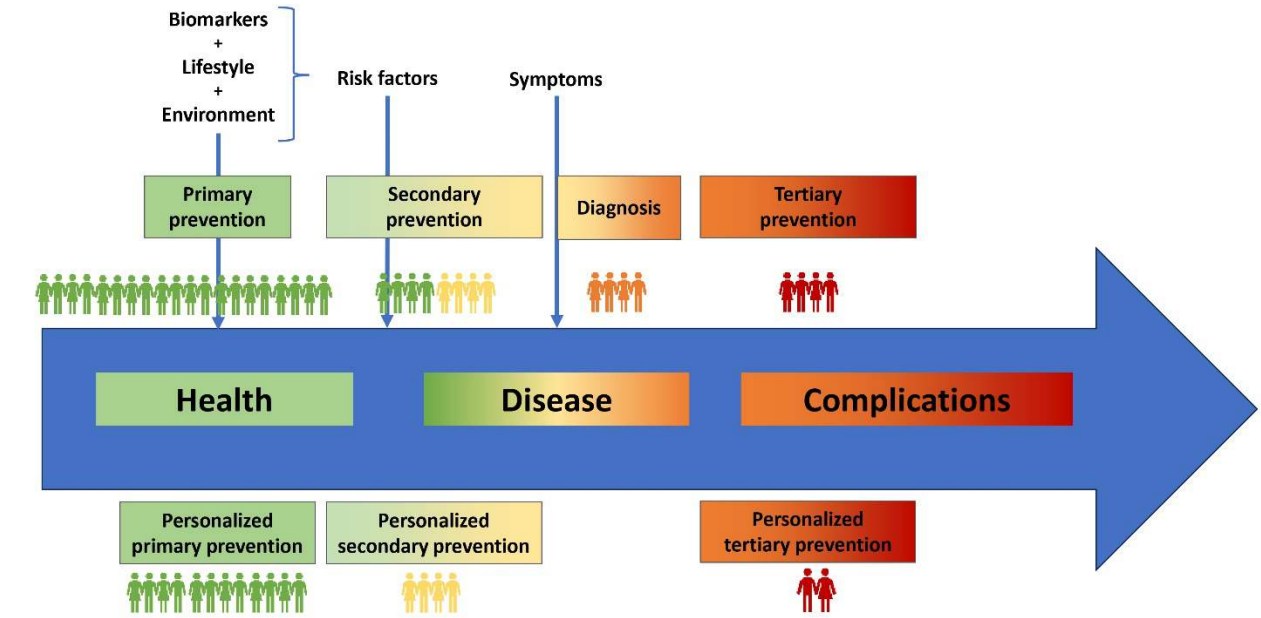

Figure 3. Description of the three levels of prevention, according to the disease stage.

The value proposition of PP is thus to use lessons from PM and to extend the precision also to health promotion and prevention. This means addressing not just the patient on the right-hand side of the figure, but also the (healthy) citizen on the left hand side of Fig. 2. However, where this is attempted in NCD behavior change interventions, a recent review found that there is no integration across the three levels of data; that biomarkers data is not used; that most interventions rely on human-led rather than automated personalisation; and that human behavior in the local context is not addressed.[19] Moving to the left from patients to citizens in Fig. 3 also increasingly requires trust in health services, governments and society [20,21], health literacy and empowerment, and community/family engagement [22] are recognized as key ingredients to change systems and behaviors, particularly as misinformation is spread, sometimes even deliberately.[23] Furthermore, we increasingly need to recognize that health behavior is shaped in a socioeconomic and cultural context, where the health sector is one of many sectors, and that e.g. the food-environment, the built-environment and the social-environment – online or in-real-life- are key shapers of health behaviors.[24]

Naturally, there is also a host of knowledge and practice gaps to plug in the biomedical and translational science area, e.g., to facilitate effective access to better predictive and diagnostic tools, which then need to be integrated into both health systems, and larger "systems for health", with appropriate policies and incentives [25]. This is where also lies our future strategic research agenda.

Knowledge gaps & challenges

Below we list a number of knowledge gaps and challenges, which in our view need to be overcome to realize PP. Some of these may lend themselves to being addressed through

"mission" approaches.[26] Missions are measurable and time-bound ambitious objectives that can help society to transform and tackle complex issues such as preventive health. By stating a mission, it is easier to design and implement purpose-oriented, solution driven approaches.

The data challenge

As in PM, ideally the potential to use different types of data in prevention is currently hampered by practical as well as legal impediments. These barriers need to be addressed in order to increase the precision both in individuals, families, population groups, or neighborhoods at increased risk, as well as to increase precision in the measures taken by more precisely/meaningfully contextualizing them. Herein lies a candidate mission, with linkages to several ongoing EU data initiatives[1] (Figure 4).

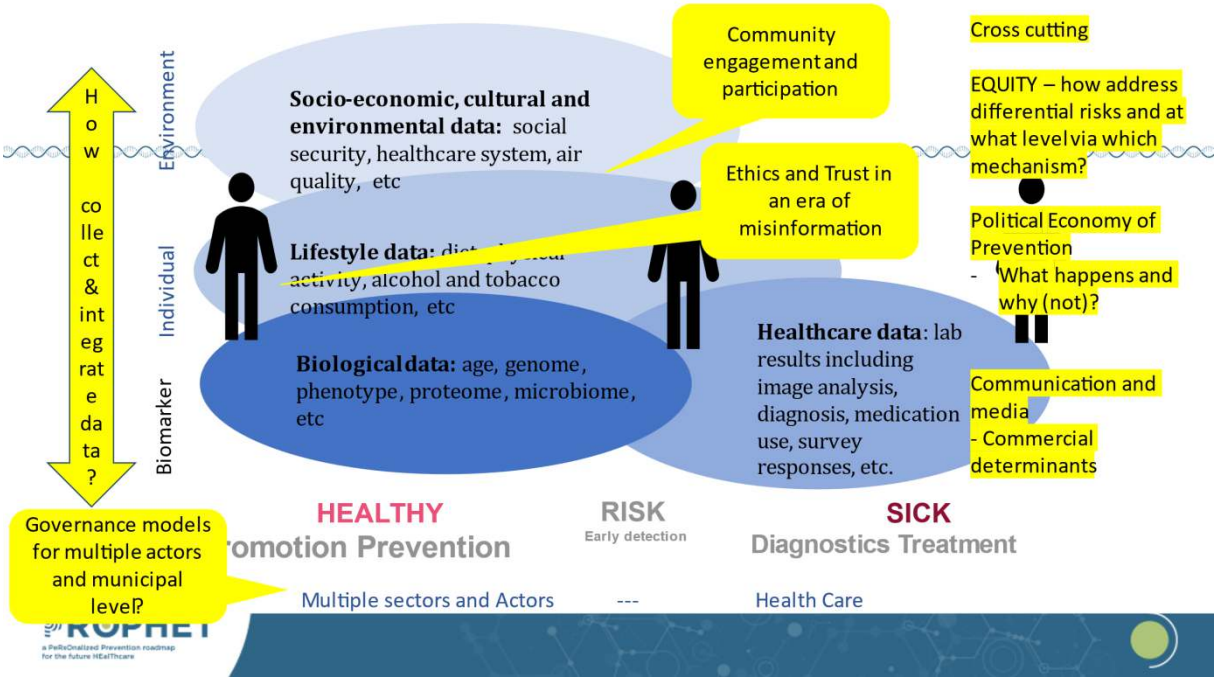

Figure 4. Selected knowledge gaps and challenges

We may also start by identifying clusters of risk factors, which may lead to several disease outcomes (e.g., cardiovascular disease (CVD), diabetes type 2, or stroke). How can individuals and population subgroups with such risk factor constellations be identified effectively, in compliance with data privacy requirements? Which of these high-risk individuals are likely to develop disease, and which will remain disease free? And which personalized-based intervention will effectively delay or reduce the risk of disease onset?[27]

In response to these open questions, the European Commission recently launched a call for proposals within the Horizon Europe program entitled " Personalized prevention of non-communicable diseases - addressing areas of unmet needs using multiple data sources" », aimed at designing new or improved ambitious policy and intervention of PP, with expected high population-wide impact on the target groups in question.[28]

[1] *e.g. data deposition, accessing, sharing, storage, GDPRs, patients' consents, ELSI, and ESFRIs, like ELIXIR and projects like B1MG and GDI*

Trust, ethics and community engagement

Public health actions can be centered on population-specific needs and outcomes assessment, policy and evidence development, and assurance of delivery of effective and ethical interventions. Crucial public health activities also include engaging communities, sharing data, building coalitions, improving genetic health literacy, and building a diverse educated workforce. All of this requires trust, which is a much-cited requirement in the field of PM and PP. But how can trust be established, and what are the determinants of trust? A conceptual model proposes three main types of trust facilitators: (1) technical, (2) ethical, and (3) institutional, all of which need further elaboration, including contextual aspects.[29] These need to be further elaborated in the SRIA .

At a societal level we need to do "surveillance" for misinformation and hesitancy, analyze it, and take appropriate action, in order to achieve population uptake of new interventions. A better understanding of cumulative cultural evolution and mechanisms underlying social contagion may be helpful to better implement preventions in the population.[30] These issues may be developed in a "Trust and Acceptance" mission.

Community engagement is increasingly realized as being key. As already done in many settings for e.g., people with diabetes through glucometers, through appropriate outreach and information, we can also empower communities to become "data collectors" and Citizen scientists.[28] In health care, e.g., family support is also extremely important in preventive and promotive work, particularly where it involves behavior change of e.g., diet or physical activity. However, innovation in prevention is required to elaborate effective and scalable forms of community and citizen engagement, where it will be important to review what has already been achieved in e.g., ELIXIR [31] and other projects. Without concerted public health action, further advances in PM with potentially broad applications could lead to further widening of health disparities in the next decade.

Behavioral Science

Ultimately PP assesses risk, which then needs to be managed, not just by the person exposed to the risk, but also by stakeholders, including health workers, who are in a position to affect risk behavior and exposure. This suggests a behavioral science research agenda, to develop an evidence-based approach to tackling risk, either for individual diseases, NCDs at large, or risk behavior [32]. Behavioral science may also inform personalization of interventions, where human behavior in the local context is not addressed.[19]

Health Sector integration and beyond

As PP interventions develop, these need to be integrated into health services. This raises a range of questions around health worker capabilities and systems support required, as well as for financing/reimbursement and incentive mechanisms to support their uptake. For NCDs the food system and food environments are key determinants, as is the built environment for physical activity and transport/energy sector for pollution.
This makes multisectoral collaboration key, where opportunities like the EU's 100 Carbon Neutral and Smart Cities by 2030 [33] provides opportunities to introduce behavioral and health outcomes into that mission driven initiative. Such multisectoral action, however, makes "multisectoral governance for health and sustainability" a key innovation area [34], at many levels of society, and particularly at municipality level.

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 so called political economy- a social science conceptualization of what gets done or not [35]. Issues for NCD prevention include how to distribute investment prevention costs across the sectors that benefit from prevention gains; and the influence of commercial market forces in policy making.[36] It was also evident during the stakeholder consultation that a stakeholder forum for multisectoral coordination and advocacy was desirable , at national as well as EU level. Such a forum could work on the "narrative" and "positioning" for prevention, and approach policymakers and stakeholders across sectors.

Furthermore, the prospect of a European Union Social Taxonomy, which requires companies to report not just on the environmental, but also social footprint, needs to be anticipated, and appropriate measures to drive financial investment in healthy living conditions need to be developed.[37]

Inequities in health and PP

Inequities in health outcomes are driven by illnesses, which in turn are driven by differential risk which is strongly linked to socio-economic factors. Therefore, measures across the spectrum of promotion, prevention and treatment also need to be adapted and highly contextualized to become precise to improve health. The nature of the inequity may be related to socioeconomic, ethnic, gender, age, or other factors, which may require different strategies to overcome.[38] A fundamental challenge to PP is of course the question "who benefits"? When it comes to PM, an increasing number of evidence-based applications that can reduce morbidity and mortality for millions of people are now available. Studies conducted in the United States have shown lower implementation rates for selected diseases with strong evidence-base applications (familial hypercholesterolemia, Lynch syndrome, hereditary breast and ovarian cancer) among racial and ethnic minority groups, rural communities, uninsured or underinsured people, and those with lower education and income.[39] In this context, a wider societal and public health agenda is needed to address disparities in implementation of PM and PP.

Scaling up- Implementation Research

Famously, new interventions are said to take 17 years to reach implementation and benefit patients.[40] While the actual time lag may vary, there are also issues around implementation fidelity and a host of operational questions to answer as interventions are put into practice in complex (health) systems. The field of implementation research addresses these questions, and PP interventions therefore need to be accompanied by a translational research agenda.[41]
Ten years ago, Schully et al reported on the continuum of translational research in cancer genetics, reporting that only a minority of the published literature was T2 research (focusing on the establishment of effectiveness in humans and clinical guidelines) or beyond, (Figure 5).[42]
In a more recent publication by Roberts et al, an analysis of investigator-initiated research grants in genomics funded between 2012 and 2016 showed that only about 1.75% of funded projects include elements related to implementation, outlining a severely deficient scenario in this area.[43]

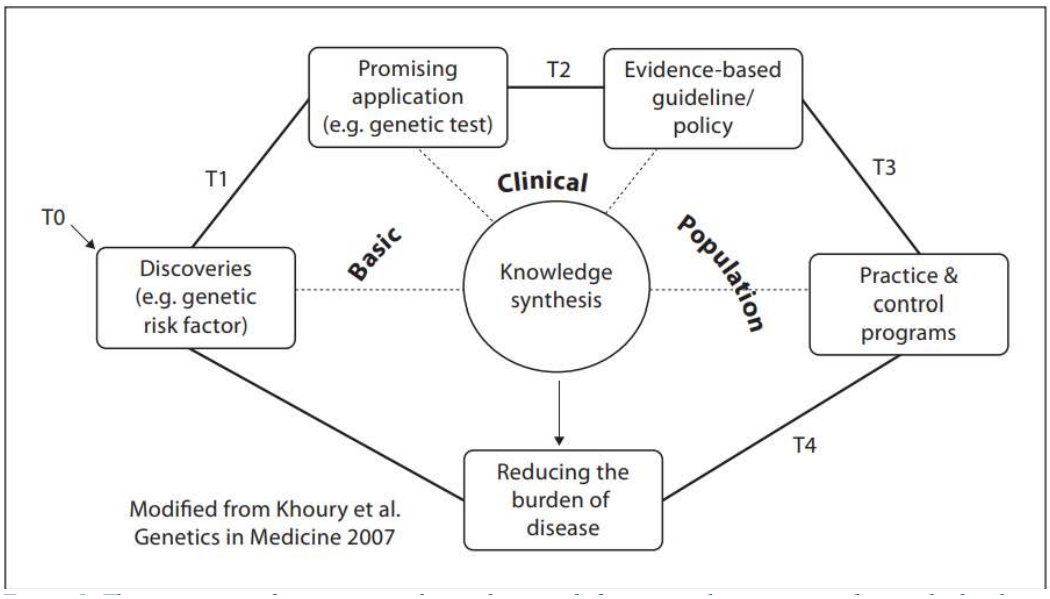

Figure 5. The continuum of genetics translational research from gene discovery to reducing the burden of disease in a population (from Schully at al, 2007)

Preliminary results of PROPHET that inform the Concept note and the future SRIA

In order to feed the **SRIA** process **development** and the stakeholder engagement process, PROPHET includes three main strands of activities: **Mapping, Assessment,** and **Building** as summarized in Figure 6.

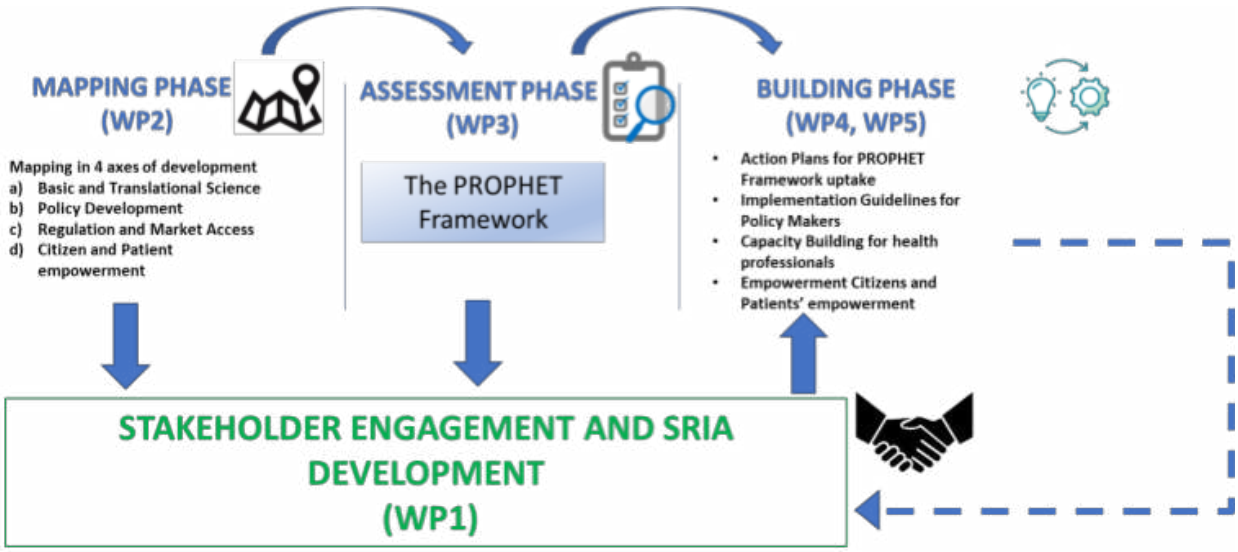

Figure 6. The PROPHET Methodology uses mapping followed by assessment and finally a building phase. All are feeding into the SRIA together with input from stakeholders.

The PROPHET action is developed along the following key drivers:
Co-creation approach, stakeholder engagement: Stakeholder engagement is a key driver in the action. The overall action governance is built around the involvement of stakeholders that will be actively engaged in the PROPHET activities and in the definition of the SRIA. A clear governance model and stakeholder engagement tools (i.e., Stakeholder Platform) will ensure a co-creative approach throughout all the project activities.
A Strategic Orientation (through SRIA) towards effective uptake and scale up: Designing of Personalized Prevention Programs should be aligned with European values and have a strategic orientation towards EU and international goals: equal access to innovative, sustainable and high-quality health care, health systems resilience, as well as improved health outcomes.
Coordinated, harmonized and comprehensive research: A coordinated process that reviews stakeholders' needs and perspectives as well as strong evidence from research is considered crucial to reach a consensus on the topics and actions necessary to develop effective approaches in Personalized Prevention.
Evidence Based Policy Making: Evidence-based policy making is necessary to support policy makers and providers of services in making better decisions and achieve better outcomes as well as increase the trust of citizens toward public decision and therefore improve the adherence of citizens to prevention programs.

PROPHET Mapping results

During the first year of the project, three mapping exercises were conducted: i) the first focused on biomarkers, encompassing both genetic and non-genetic markers available for risk stratification in major chronic diseases; ii) the second explored personalized prevention approaches and the barriers that restrict their implementation, and iii) the third examined clinical utility and its indicators for genetic and omic testing. The key findings from these mappings, essential for the project's advancements, are detailed in the following paragraphs.

Mapping of the available biomarkers, including genetics, for risk prediction and stratification in cancer, cardiovascular and neurodegenerative diseases and their potential integration with digital technologies [44]

One of the tools that technological advances may add to promote personalized prevention for chronic diseases is the identification and validation of new biomarkers that may help to better identify subgroups of individuals with different risks of having the disease, that eventually could improve prevention strategies at the individual level. To provide a research landscape of the biomarkers that are available or under development, three rapid scoping reviews were conducted in parallel, based on a common protocol adapted to each specific condition (cancer, cardiovascular or neurodegenerative diseases which were chosen in the beginning of the project to represent different disease fields and because they are quite common.).
The most prolific field of biomarker research for primary or secondary prevention is in cancer, followed by CVD (843 papers on cancer, 775 articles on CVD). In contrast, for neurodegenerative diseases the number of articles is considerably lower, less than a third of those found in cancer (286 articles).

- Cancer: primary prevention research for cancer is mainly focused on molecular biomarkers (mostly genetic), while imaging biomarkers are more prominent in the secondary prevention papers identified. There was limited research on biomarkers for primary/secondary prevention of corpus uteri, bladder, and kidney cancer compared to other types of cancer.
- Cardiovascular disease: molecular biomarkers, especially in ischemic heart disease (IHD) and stroke, the leading causes of CVD death, are the most commonly researched. In primary prevention most research activity is for IHD and stroke within general and high-risk CVD populations and for the molecular/genomics and imaging biomarker categories. In secondary prevention, most research activity is in IHD and stroke within general and high-risk CVD populations and for the molecular/biochemistry (biochemical) and imaging biomarker categories.
- Neurodegenerative disorders: the most notable finding is the considerable focus on Alzheimer's disease. In contrast, there is a scarcity of available research for other neurodegenerative diseases, specifically Lewy body disease and frontotemporal dementia. The research on Alzheimer's disease was primarily for secondary prevention strategies, whilst for the other diseases it was focused on primary prevention. Molecular biomarkers were a major focus of the research in neurodegenerative diseases.

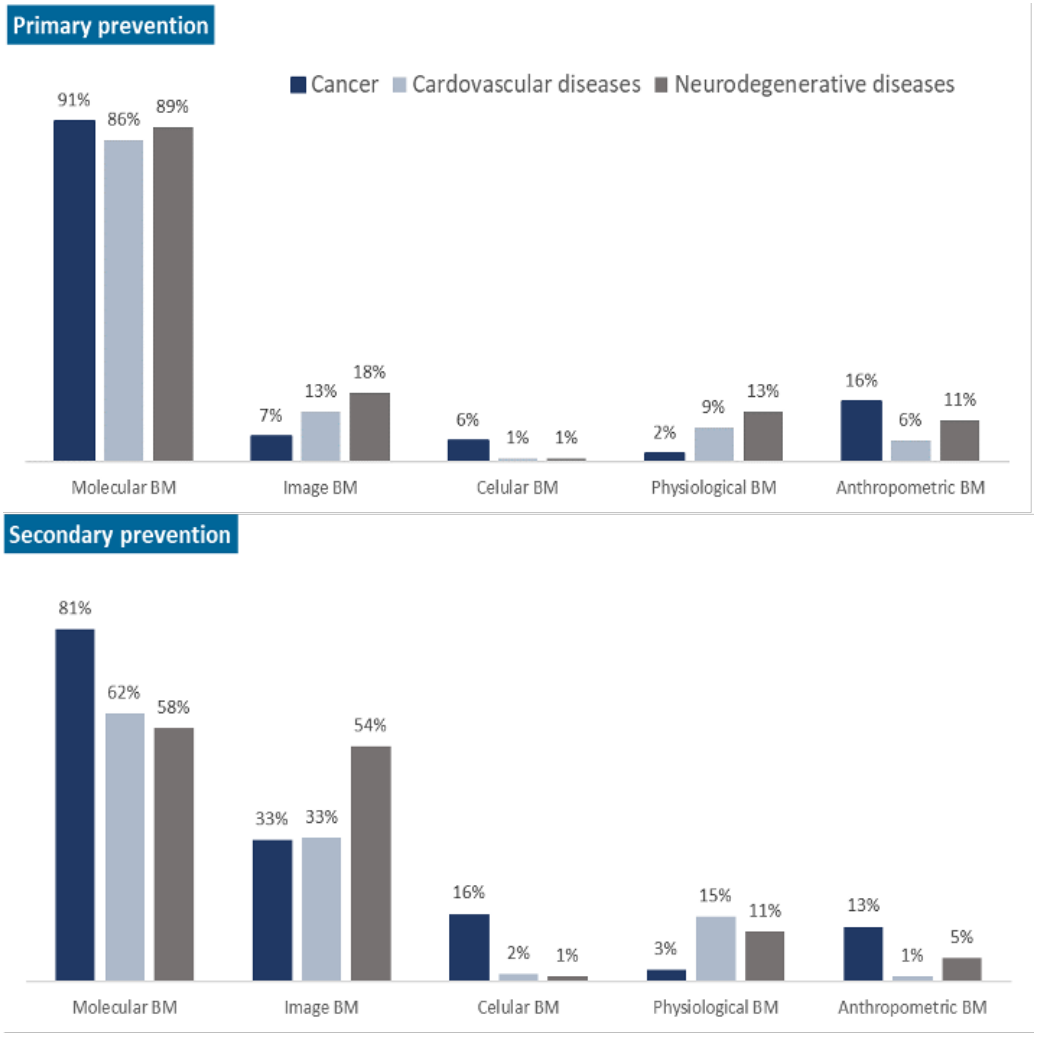

Figure 7. Percentage of studies by biomarker category in primary and secondary prevention within each group of diseases

Molecular biomarkers' research dominates across all three disease groups. Imaging biomarkers are the next most investigated, except for cancer, where anthropometric measures (in particular BMI) were more frequently explored. Imaging biomarkers are more relevant in secondary prevention, especially in neurodegenerative diseases. Cellular biomarkers are mostly limited to cancer studies, while physiological biomarkers are used relatively more in secondary prevention of CVD than in other diseases. Biochemical biomarkers were the second most researched in primary prevention, and the most common in secondary prevention. In contrast, there was very limited research for epigenetic or microbiome-based biomarkers. Of note, it was relatively uncommon to see studies that specifically explored the interaction between different modifiable factors and genetic biomarkers (Fig. 7).

As the use of biomarkers in health is mainly focused on treatment, it is crucial to undertake further research in the identification, evaluation and validation of different biomarkers for personalized primary and secondary prevention for cancer, cardiovascular diseases and neurodegenerative disorders in public health settings, as well as pilot studies to explore the effectiveness of those strategies that would be applied to a specific population.

However, while many biomarkers are now classified as of primary prevention relevance, it is not apparent that a correlation in risk implies that the marker has the potential to become a prevention intervention, or program. The added value of additional information – of whatever source or type- needs to be evaluated for its clinical utility, and incremental cost-utility over and beyond the present interventions and programs, see further below.

Mapping the-state-of-the-art and bottlenecks for the adoption of personalized prevention approaches in Health Systems [45]

One of the primary areas explored through the mapping is the state-of-the-art of personalized prevention in Europe and beyond, and the bottlenecks that hinder the complete integration of these approaches within healthcare systems.

To comprehensively identify approaches, bottlenecks and challenges, the project adopted a methodology which encompasses a scoping review, conducted on scientific and grey literature, interviews and surveys for end users and a variety of stakeholders, such as healthcare professionals, policymakers, and other pertinent parties.

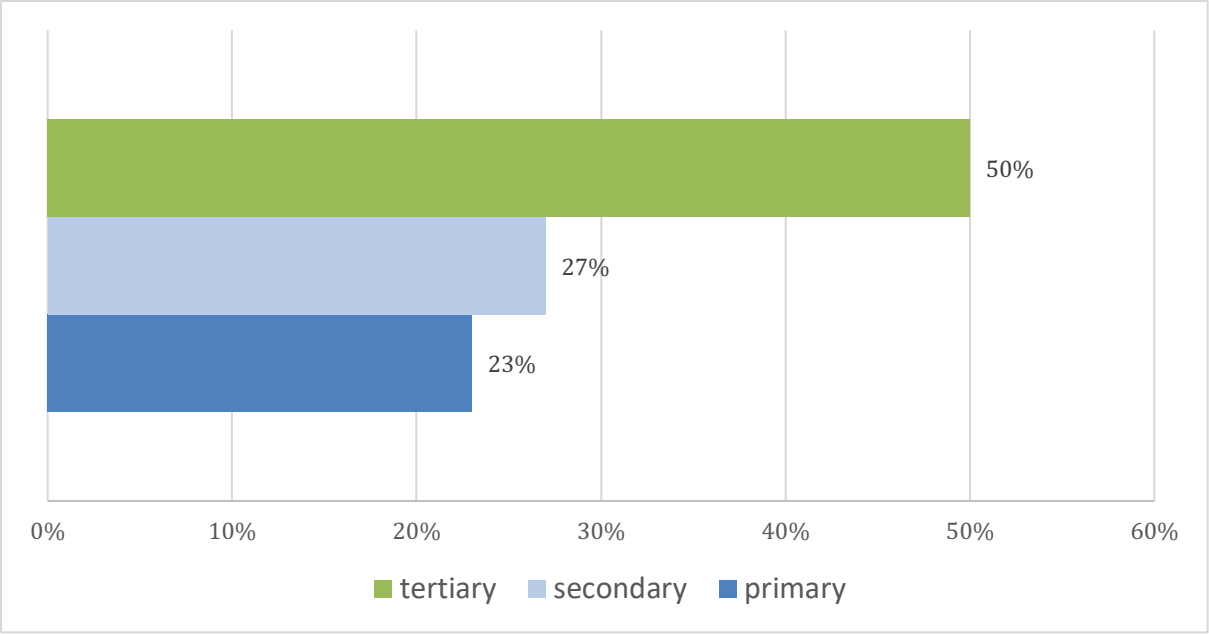

Figure 8. Proportion of the levels of prevention among the personalized prevention approaches identified.

The literature review has revealed a diverse landscape of personalized prevention strategies. From the total of 98 records included, more than half- of the strategies are categorized as tertiary prevention. This indicates a noteworthy emphasis on interventions targeting individuals already impacted by certain conditions. One plausible interpretation lies in the heightened investment usually allocated to therapeutic interventions. Moreover, the feasibility of implementing genetic testing and related preventive strategies in individuals already afflicted with illnesses contributes to the prominence of tertiary prevention. These individuals possess an increased awareness of risks and diseases, thereby facilitating the integration of customized interventions into their care plans. Another reason is the different efficacy of certain treatments according to the metabolic profile of the patient (pharmacogenomics). Within the spectrum of personalized prevention, less than a third of identified approaches are attributed to secondary prevention, concentrating on individuals deemed at high risk of developing specific conditions due to their risk factors. This aligns with the proactive nature of secondary prevention, driven by the presence of various screening programs and the increased emphasis on early detection and

intervention. However, given that secondary prevention targets asymptomatic individuals potentially at risk of developing a disease, engaging this group could indeed pose challenges, which might hinder achieving optimal adoption levels.

Conversely, primary prevention constitutes the minority of the identified approaches and is directed at averting the onset of diseases in generally healthy individuals, by considering their risk factors (biomarker, lifestyle and environment). This lower percentage could potentially be attributed to the intricate challenges associated with influencing lifestyle behaviors and risk factors within a broader population. As well as the often quite poor predictive value of the risk methods that have so far been employed for primary prevention of NCDs.

The findings from this comprehensive review highlight a strong focus on cancer prevention, aligning with a deeper understanding of the genetic factors influencing cancer susceptibility, compared to other diseases. Indeed, conditions like cardiovascular diseases and metabolic disorders were less represented in the review. This discrepancy is indicative of a well-established awareness of the significant influence of lifestyle factors on these diseases, underscoring the importance of addressing personal choices when shaping personalized prevention strategies. An even lower percentage of the identified approaches, however, pertains to neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, or psychiatric disorders, such as major depressive disorder. This underscores the continued lack of adequate understanding and attention toward these conditions, despite their significant burden on healthcare systems, as currently more than 55 million people worldwide live with dementia and, according to data from 2019, 970 million people with a mental disorder (Fig. 9) [2,46].
Nevertheless, despite the wealth of insights into personalized prevention approaches, their current implementation within healthcare systems is lacking. Several interconnected barriers, identified from literature and stakeholder consultations, contribute to this gap. From the literature scoping review, out of the 220 articles included, 24 main bottlenecks were identified and traced in 5 main categories:

1. Research
2. Technologies
3. Healthcare workers
4. ELSI and Implementation
5. Citizens and patients

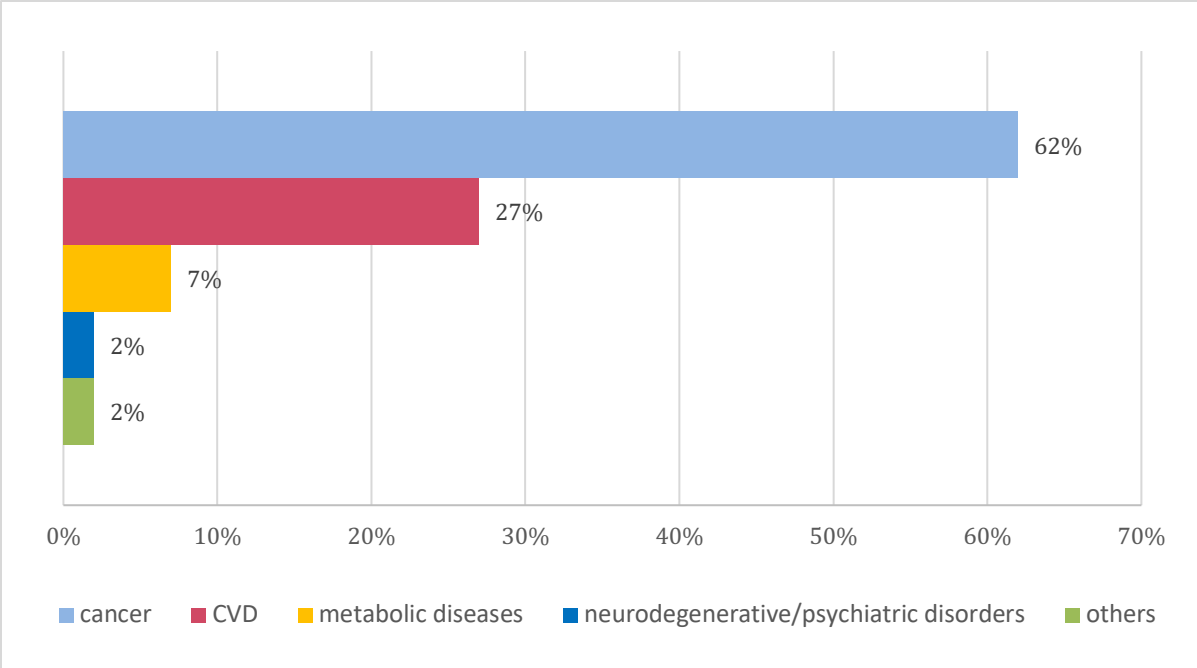

Figure 9. Proportion of chronic diseases among personalized prevention approaches identified

From the interviews, 5 main levels of barriers for a wider adoption of personalized prevention were identified:

a. Healthcare system: refers to the main cross-cutting components of a healthcare system, based on the WHO healthcare system building blocks framework.[47,48]
b. Research: refers to the main components of the research and innovation sector.
c. Implementation: refers to the multiple processes and activities associated with the translation of scientific findings to clinical practice.
d. Awareness, education and literacy: refers to understanding and competences of each of the stakeholder groups regarding personalized prevention.
e. Personal attitudes: refers to individual attitudes of end-users, such as citizens, patients, and healthcare professionals, to personalized prevention.

After analyzing the initial 200 survey responses, a remarkable consistency was found between the barriers identified by the literature and the interviewed experts. Overall, there were four main areas that were highlighted as barriers, and that have cascading implications for adoption of personalized prevention:

- Health systems are fully geared towards care and not towards prevention. This has enormous implications for the development of strategies for personalized prevention, for funding and adequate resources, for reimbursement processes and equity of access, and for incentives for research, all of which were highlighted as barriers for personalized prevention.

- Awareness and understanding of the personalized prevention concepts are low for all stakeholder groups, explicitly acknowledged by citizens and patients, policy makers and health professionals, but also apparent in the neutral opinions to some questions by

researchers. The implications of this lack of awareness and understanding are different for the different stakeholder groups but warrant urgent tackling.

- The lack of basic and life-long training for health professionals, of actions to document and raise interest of policy makers, as well as of a true interest in improving health literacy of citizens and patients are also main challenges.

- Insufficient evidence of cost-efficiency, of research, of regulation for translation were also highlighted as main issues to be addressed that will have a major impact in the change of health systems focus from care to prevention.

These main barriers are interconnected and must be addressed together for an effective solution. Many are not specific to personalized prevention but are common for prevention, across different levels . Many are also not specific to personalized prevention, but to personalized medicine in general. So, seeking solutions that will open the way for true adoption of personalized prevention will require a concerted effort to increase the visibility of this concept and to engage all stakeholders in a shared mission to seamlessly integrate personalized prevention into health systems, across the WHO six health systems building blocks: Leadership and governance, Service delivery, Health system financing, Health workforce, Medical products, vaccines and technologies, and Health information systems [47,48].

List of process and outcome indicators for the evaluation of the clinical utility of personalized preventive approaches [49]

One of the main objectives of PROPHET is to develop a multidimensional framework for appraising and adopting personalized preventive approaches in health systems starting with the identification of indicators that are used in the evaluation of genetics and genomics technologies. A preliminary analysis of the literature revealed variations in the usage of the term *"clinical utility"* across different countries and stakeholders, indicating a lack of consensus on key evaluation elements for genomic technologies. Most experts agreed on some key dimensions for evaluating genetic and genomic technologies, such as the technical characteristics of a test, prognostic and predictive abilities of the test. However, the incorporation of other dimensions, like the impact on equity or the personal value of the information provided by the test, was more frequently omitted and not included in all types of assessments. In our research, we identified the reports of the assessments of genetic tests with the main goal of collecting and analyzing the indicators used within these. A total of 57 formal assessments of genetic and genomics technologies and 148 indicators were identified (Fig 10).

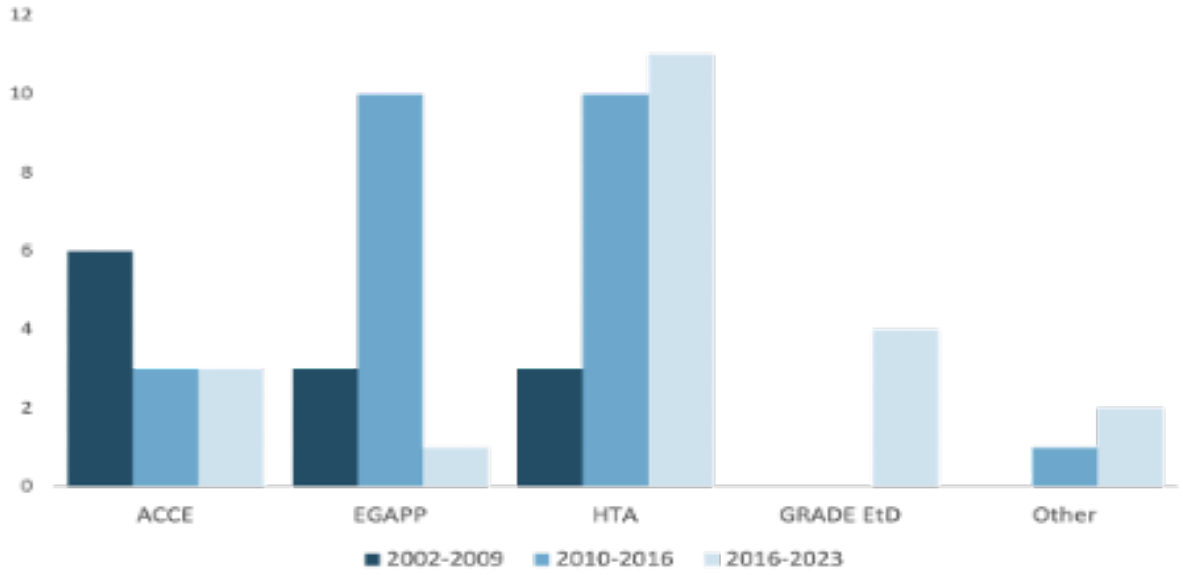

Figure 10. Number of documents by assessment methodology and publication year

The analysis of these assessment documents has provided significant insights into the current state of evaluating genetic and genomic technologies used in prevention. In the early 2000s, with the development of the ACCE (Analytic Validity, Clinical Validity, Clinical Utility, Ethical legal and social issues) framework, the evaluation of genetic and genomic technologies utilized specific frameworks tied to the classic dimensions commonly employed in this field. However, from 2010 onwards, the evaluation of these technologies appears to have become more standardized, aligning with common assessment methodologies such as health technology assessments (HTA), which gives greater importance to economic evaluations and modeling analyses. Presently, HTA continues to be widely used, in line with the efforts of the European Union to establish it as the primary methodology for assessing the implementation of health technologies. Despite the prevalence of HTA, other novel assessment methods, such as GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence to Decision (EtD) frameworks, are also being employed. This may be attributed to the fact that these methods consider other dimensions closely tied to technology implementation, such as feasibility. The analysis of the indicators also revealed that, even for some dimensions defined by most assessments as key dimensions, such as health outcome and economic impact, the lack of relevant literature data leads to the evaluation of evidence derived from modelling or indirect evidence (Fig. 11).

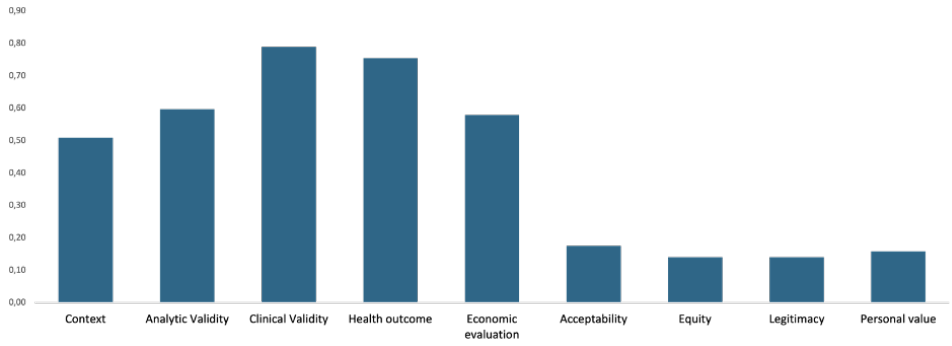

Figure 11. Proportion of the assessments that had at least one indicator in each of the dimensions

Indeed, it is imperative to invest increased scientific and economic efforts to ensure the production of robust evidence for the most promising technologies in the field of genetics. Simultaneously, achieving a broader consensus on how to use and evaluate readily available evidence in the context of genetic technologies is equally crucial.

Towards the PROPHET Strategic Research and Innovation Agenda (SRIA)

Within the PROPHET project, our mission is to craft a SRIA centered on personalized prevention. The primary goal of this SRIA is to promote the development of innovative, sustainable, and highly effective personalized programs designed to prevent chronic diseases.

The fundamental value of the PROPHET SRIA will lie in its ability to translate our project's vision into a holistic, long-term systemic approach. By directly contributing to the realization of the ICPerMed Vision [50], our SRIA will be connected to a broader European landscape. It will draw inspiration from the EPPerMed (European Partnership for Personalized Medicine) SRIA[51], the initiative under Horizon Europe dedicated to maximizing the potential of personalized medicine approaches. While EPPerMed casts a wide net, our PROPHET SRIA will stand out with a sharp focus on personalized prevention.

This focused approach directly addresses the unique needs and challenges of personalized prevention, contributing to a more targeted outcome. This outcome aims to provide comprehensive guidelines for designing and evaluating personalized prevention approaches, delving into all the necessary aspects for their implementation. These aspects encompass the necessary evidence also from a clinical point of view, methodologies for assessment and implementation, as well as engagement strategies for professionals and stakeholders.

A significant aspect of the PROPHET project lies in its co-creative approach, engaging a diverse and extensive group of stakeholders deeply embedded in the field of personalized medicine, particularly personalized prevention. Stakeholder engagement is pivotal, propelling the project through all phases of SRIA development.

The essence of the SRIA stems from a collective and forward-looking co-creation process, identifying and prioritizing based on evidence emerging from the PROPHET activities and complementary experiences at various levels — EU, national, and institutional. This collaborative approach will ensure the SRIA's content is robust and well-aligned with the needs of the stakeholders involved (Figure 12).

The path towards the SRIA begins with the release of this concept paper and a subsequent workshop where the concept will be presented (Valencia meeting October 2023), where partners and key stakeholders collaborate to discuss the concept and the preliminary PROPHET results, providing crucial inputs for the full SRIA development.

After this first step, the consortium will pave the way for the release of the first version of the SRIA. The consortium, thanks to the scientific work produced in the WPs, will select areas of action and prepare a Delphi consultation in order to define key priorities and actions vital for a strategy on personalized prevention. Anticipated milestones mark the trajectory of this initiative. In April 2024, a final workshop on WP2 (Literature Mapping and Research Gap Analysis on Basic and Translational Sciences in Personalized Prevention) will be conducted online. Right after that, the Delphi process will commence. By September 2024, the first version of the SRIA will be published, followed by a public consultation in the second half of 2024 on the draft version. The responses from this consultation will shape the final version of the SRIA, expected to be available in September 2025.

The SRIA and the comprehensive PROPHET framework will serve as a standard, supporting the definition of knowledge-based and people-centered Personalized Prevention programs. The scientific validity and co-creation approach applied in developing the SRIA and the PROPHET

framework will gather significant support from major EU and international stakeholders, ensuring its effective utilization and implementation.

Moreover, the SRIA and the outcomes from the “Mapping” and “Assessment” strand offer crucial inputs to bolster the "Building" strand activities (Figure 6). This holistic approach forms the cornerstone of the project, harmonizing vision with practical application, and navigating the path toward a future where personalized prevention becomes a tangible reality, making a profound impact on public health and well-being.

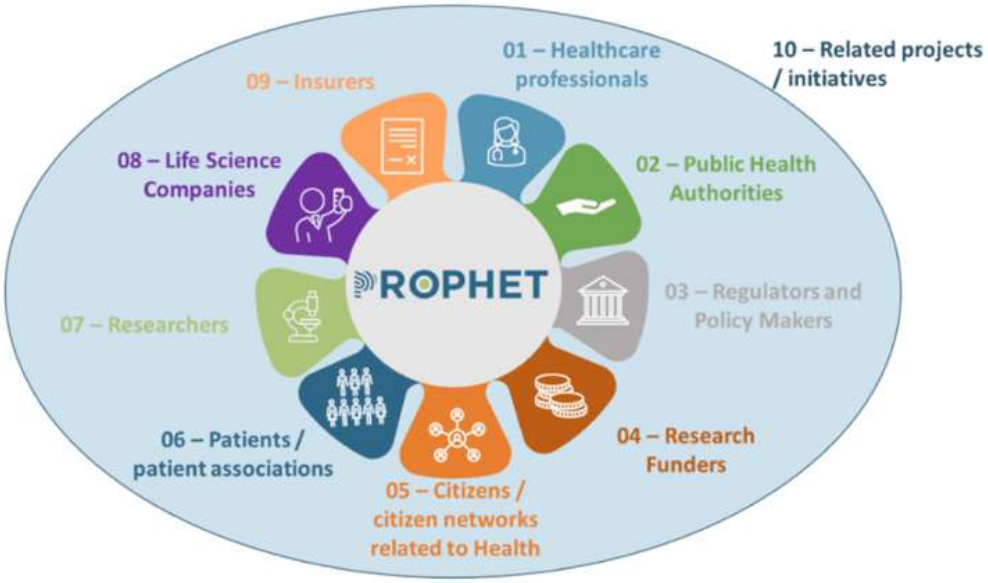

Figure 12. PROPHET Stakeholders identified for SRIA co-creation

References

1. World Health Organization. The Global Health Observatory, Indicator Metadata Registry List [Internet]. [cited 2023 Sep 25]. Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3411

2. Global Burden of Disease Collaborative Network, Global Burden of Disease Study 2019 (GBD 2019) Results (2020, Institute for Health Metrics and Evaluation – IHME) https://vizhub.healthdata.org/gbd-results/

3. Budreviciute A, Damiati S, Sabir DK, Onder K, Schuller-Goetzburg P, Plakys G, Katileviciute A, Khoja S, Kodzius R. Management and Prevention Strategies for Non-communicable Diseases (NCDs) and Their Risk Factors. Front Public Health. 2020 Nov 26;8:574111. doi: 10.3389/fpubh.2020.574111. PMID: 33324597; PMCID: PMC7726193.

4. Santos AC, Willumsen J, Meheus F, Ilbawi A, Bull FC. The cost of inaction on physical inactivity to public health-care systems: a population-attributable fraction analysis. Lancet Glob Health. 2023;11:e32–9.

5. https://ncdalliance.org/why-ncds/NCDs

6. European Commission. PROPHET Project [Internet]. [cited 2023 Sep 25]. Available from: https://prophetproject.eu

7. Love-Koh J, Peel A, Rejon-Parrilla JC, Ennis K, Lovett R, Manca A, et al. The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. Pharmacoeconomics. 2018;36:1439–51.

8. Garattini L, Curto A, Freemantle N. Personalized medicine and economic evaluation in oncology: all theory and no practice? Expert Rev Pharmacoecon Outcomes Res. 2015;15:733–

9. European Commission. PRECeDI [Internet]. [cited 2023 Sep 25]. Available from: https://ephconference.eu/repository/projects/Final_Recommendations_How_to_integrate_Personalized_Medicine_into_Prevention.pdf

10. Gillman MW, Hammond RA. Precision Treatment and Precision Prevention. JAMA Pediatr. 2016;170:9.

11. Vineis P, Wild CP. The science of precision prevention of cancer. Lancet Oncol. 2017;18:997–8.

12. Strömberg U. How can precision prevention be approached from a general population perspective within the field of cancer epidemiology? Acta Oncol (Madr). 2021;60:1272–4.

13. WHO. World Health Assembly Adopts More Best Buys to Tackle NCDs, Reconfirms Impact of Alcohol Policy Best Buys [Internet]. [cited 2023 Sep 25]. Available from: https://movendi.ngo/news/2023/06/01/world-health-assembly-adopts-more-best-buys-to-tackle-ncds-reconfirms-impact-of-alcohol-policy-best-buys/#:~:text=WHO%27s%20“Best%20Buys”%20are%20policy,and%20lack%20of%20physical%20activity.

14. WHO. ANNUAL REPORT OF THE ALLIANCE FOR HEALTH POLICY AND SYSTEMS RESEARCH [Internet]. 2022. Available from: https://iris.who.int/bitstream/handle/10665/367104/9789240070721-eng.pdf

15. Bensberg M, Joyce A, Wilson E. Building a Prevention System: Infrastructure to Strengthen Health Promotion Outcomes. Int J Environ Res Public Health. 2021;18:1618.

16. Ricciardi W, Boccia S. New challenges of public health: bringing the future of personalised healthcare into focus. Eur J Public Health. 2017;27:36–9.

17. Rose G. Strategy of prevention: lessons from cardiovascular disease. BMJ. 1981;282:1847–51.

18. Thomas DC. What Does "Precision Medicine" Have to Say About Prevention? Epidemiology. 2017;28:479–83.

19. Mauch CE, Edney SM, Viana JNM, Gondalia S, Sellak H, Boud SJ, et al. Precision health in behaviour change interventions: A scoping review. Prev Med (Baltim). 2022;163:107192.

20. Gilson L, Palmer N, Schneider H. Trust and health worker performance: exploring a conceptual framework using South African evidence. Soc Sci Med. 2005;61:1418–29.

21. Min J. Does social trust slow down or speed up the transmission of COVID-19? PLoS One. 2020;15:e0244273.

22. Klingberg S, van Sluijs EM, Draper CE. Parent perspectives on preschoolers' movement and dietary behaviours: a qualitative study in Soweto, South Africa. Public Health Nutr. 2021;24:3637–47.

23. Lee SJ, Lee C-J, Hwang H. The impact of COVID-19 misinformation and trust in institutions on preventive behaviors. Health Educ Res. 2023;38:95–105.

24. George G, Dilworth-Bart J, Herringa R. Potential Socioeconomic Effects of the COVID-19 Pandemic on Neural Development, Mental Health, and K-12 Educational Achievement. Policy Insights Behav Brain Sci. 2021;8:111–8.

25. Systems for health: everyone has a role (who.int)

26. European Commission. Mission-oriented policy studies and reports [Internet]. [cited 2023 Sep 25]. Available from: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/mission-oriented-policy-studies-and-reports_en

27. Yacamán Méndez D, Zhou M, Trolle Lagerros Y, Gómez Velasco D V., Tynelius P, Gudjonsdottir H, et al. Characterization of data-driven clusters in diabetes-free adults and their utility for risk stratification of type 2 diabetes. BMC Med. 2022;20:356.

28. EU-Citizen.Science https://eu-citizen.science/ Accessed October 1, 2023

29. Afua Adjekum, Marcello Ienca, and Effy Vayena.What Is Trust? Ethics and Risk Governance in Precision Medicine and Predictive Analytics.OMICS: A Journal of Integrative Biology.Dec 2017.704-710.http://doi.org/10.1089/omi.2017.0156

30. Olsson A, Knapska E, Lindström B. The neural and computational systems of social learning. Nat Rev Neurosci. 2020;21:197–212.

31. ELIXIR | A distributed infrastructure for life-science information (elixir-europe.org)

32. David P. French, Amy L. Ahern, Colin J. Greaves, Rhiannon E. Hawkes, Suzanne Higgs, Rachel Pechey, Falko F. Sniehotta Preventing type 2 diabetes: A research agenda for behavioural science; Diabetic MedicineVolume 40, Issue 8 e15147 https://doi.org/10.1111/dme.15147

33.Climate-neutral and smart cities (europa.eu)

https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/climate-neutral-and-smart-cities_en

34. Ottersen OP, Dasgupta J, Blouin C, Buss P, Chongsuvivatwong V, Frenk J, et al. The political origins of health inequity: prospects for change. The Lancet. 2014;383:630–67.

35. Shiffman J. Four Challenges That Global Health Networks Face. Int J Health Policy Manag. 2017;6:183–9.

36. The Lancet. Unravelling the commercial determinants of health. The Lancet. 2023;401:1131.

37. Celsia. EU Social Taxonomy: What does it mean for your business? 2022 [cited 2023 Sep 25]; Available from: https://www.celsia.io/blogs/what-is-the-social-taxonomy#:~:text=%E2%80%8D-,What%20is%20the%20EU%20social%20taxonomy%3F,sustainable%20finance%20and%20sustainable%20governance.

38. Griffith DM. Preface: Precision Medicine Approaches to Health Disparities Research. Ethn Dis. 2020;30:129–34.

39. Khoury MJ, Bowen S, Dotson WD, Drzymalla E, Green RF, Goldstein R, Kolor K, Liburd LC, Sperling LS, Bunnell R. Health equity in the implementation of genomics and precision medicine: A public health imperative. Genet Med. 2022 Aug;24(8):1630-1639. doi: 10.1016/j.gim.2022.04.009.

40. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med. 2011;104:510–20.

41. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Republished research: Implementation research: what it is and how to do it. Br J Sports Med. 2014;48:731–6.

42. Schully SD, Benedicto CB, Gillanders EM, Wang SS, Khoury MJ. Translational Research in Cancer Genetics: The Road Less Traveled. Public Health Genomics. 2011;14:1–8.

43. Roberts MC, Clyne M, Kennedy AE, Chambers DA, Khoury MJ. The current state of funded NIH grants in implementation science in genomic medicine: a portfolio analysis. Genetics in Medicine. 2019;21:1218–23. 44. Elena Plans-Beriso. Biomarkers for personalized prevention of chronic diseases: protocol of a rapid scoping review [Internet]. [cited 2023 Sep 26]. Available from: https://osf.io/7jrwd

45. Sara Farina. Mapping the state-of-the-art and bottlenecks for the adoption of personalized preventive approaches in Health Systems in Europe and beyond: a study protocol [Internet]. [cited 2023 Sep 26]. Available from: https://osf.io/m4sz3

46. WHO. Dementia. [Internet] 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/dementia

47. World Health Organization. (2010). Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies. World Health Organization. https://iris.who.int/handle/10665/258734

48. Systems thinking (who.int) https://ahpsr.who.int/what-we-do/thematic-areas-of-focus/systems-thinking

49. Angelo M. Pezzullo, Angelica Valz Gris. Process and outcome indicators for the evaluation of the clinical utility of personalized preventive approaches: a scoping review [Internet]. [cited 2023 Sep 26]. Available from: https://osf.io/h3cxn

50. ICPerMed. The ICPerMed vision for 2030 [Internet]. 2019. Available from: https://www.icpermed.eu/media/content/Vision_Paper_2019.pdf

51. ICPerMed. The Strategic Research & Innovation Agenda (SRIA) for Personalised Medicine (PM) [Internet]. 2023 Apr. Available from: https://www.icpermed.eu/media/content/EPPerMed-SRIA.pdf

*** LIST OF PARTNERS WHO PARTICIPATED IN THE DRAFTING:**

Stefan Swartling Peterson (KI)
Carl Johan Sundberg (KI)
Ingrid Kockum (KI)
Alexandra Gyllenberg (KI)
Jhon Alvarez Ahlgren (KI)
Evelina Flodkvist (KI)

Stefania Boccia (UCSC)
Roberta Pastorino (FPG)
Tommaso Osti (UCSC)
Sara Farina (UCSC)

Charlotte Alcouffe (GAC)

Peter Mills (PHGF)
Laura Blackburn (PHGF)

Magda ChegKazi (ELIXIR)
Claudia Louati (EPF)
Valentina Strammiello (EPF)

Marina Pollan (ISCIII)

Anu Reigo (UTARTU)

Carla Val El (VUMC)

Eva Van Steijvoort (KUL)

Alexandra Costa (INSA)