Fundación InstitutoRoche

THE VALUE OF PERSONALIZED PRECISION MEDICINE IN THE SUSTAINABILITY AND EFFICIENCY OF THE HEALTHCARE SYSTEM

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CONTENT

EXECUTIVE SUMMARY

The sustainability and efficiency of the healthcare system are essential for ensuring equitable access to medical care, improve public health, and optimize the use of available resources. However, healthcare systems face the challenge of limited resources, while pharmaceutical spending and healthcare demand are continuously increasing. Therefore, the focus has been placed on the optimization and personalization of the clinical approach, in order to guarantee the quality, effectiveness, and efficiency of healthcare systems within the constraints of public budgets.

In this regard, **Personalized Precision Medicine** represents a paradigm shift in patient care by enabling a personalized preventive, diagnostic, therapeutic, follow-up and monitoring approach, which is more effective and safer for each patient. It also contributes to optimizing health care and management processes. Consequently, its clinical application offers a clear **opportunity to significantly improve patient health outcomes**, while **ensuring the sustainability and efficiency of the healthcare system**, positioning it as a key element to **transform the healthcare system**.

Based on an analysis of the elements necessary for sustainability and efficiency, this report has been prepared in order to contribute to highlighting and valuing those areas of application of Personalized Precision Medicine in which it would add value in terms of contribution to the sustainability and efficiency of the healthcare system. To this end, initiatives and specific examples of the successful implementation of Personalized Precision Medicine have been analyzed, with the support and insights of a working group composed by a multidisciplinary team with wide experience in different areas related to Personalized Precision Medicine.

Main conclussions of the report:

Achieving sustainability and efficiency in the healthcare system, requires balancing health outcomes and financial and social aspects, ensuring quality of life, health, equity, and patient satisfaction.

This implies a **shift in the system's orientation**, promoting disease prevention and integrated care at all levels, focused on patient needs. To do this, it is necessary to have resources available, not only material but also economic, human, and IT, in a healthcare context that must embrace **digital transformation**, which is essential for optimizing and automating processes.

Furthermore, collaborative work that allows sharing of efforts, resources, and knowledge must be the basis that drives **research** for the development of technologies and innovations and its translation into clinical practice. On the other hand, **education at all levels** (general population, healthcare personnel, managers, etc.) is crucial to ensure **proper planning** that addresses the current complexity and fragmentation of the healthcare system, as well as the development of an appropriate **regulatory and ethical framework**, adapted to technological and scientific advances, that guarantees and safeguards equity. All of this can be achieved through the implementation of Personalized Precision Medicine.

Personalized Precision Medicine can contribute to the sustainability and efficiency of the healthcare system by improving the efficacy, effectiveness, and efficiency of treatments; reducing the toxicity and adverse effects of medications and the consequences of diseases; and improving and reducing disparities in health outcomes of healthcare interventions, **adding value in its areas of application**:

- **Research**: it allows for a better understanding of the different biological mechanisms and molecular bases that cause diseases, contributing to the identification of biomarkers and potential therapeutic targets through new designs and strategies research.
- **Risk Prediction and Disease Prevention**: thanks to the holistic vision that Personalized Precision Medicine offers of individuals, it would facilitate the prediction of disease development risk, as well as its primary, secondary, and tertiary prevention.
- **Screening and Precision Diagnosis**: hand in hand with omics technologies and the digital transformation of the healthcare system, would allow the identification of biomarkers for screening, stratification, and patient diagnosis.
- **Personalized treatment**: The possibility of integrating pharmacogenomic profile information with the clinical information of each patient or groups of patients would allow the customization of treatment based on individual variability in response to medications.
- **Follow up and Monitoring**: Personalized Precision Medicine provides insights about biomarkers and surrogate markers linked to the progression or prognosis of diseases, which is essential for early detection of changes in their progression and anticipating possible declines in people's health.

- **Health care and Management**: greater knowledge of diseases and patient needs would contribute to adapting health care and management to the integrated and holistic vision of health, for the reorganization of resource utilization.

However, there are **limitations** that need to be addressed to achieve sustainability and efficiency of the healthcare system, in the context of Personalized Precision Medicine, such as the **absence of health outcome measurement and evaluation of investments made in the healthcare system**, or the need to **ensure the availability of resources**, such as human or technological resources, without compromising the needs of the future.

ACKNOWLEDGEMENTS

Thank you for your collaboration and commitment to the **working group** composed of the coordinator and the panel of experts who have contributed to the development of the project and the preparation of this document. Thank you for sharing your knowledge and perspective on how Personalized Precision Medicine contributes to the sustainability and efficiency of the future healthcare system, as well as your proposed recommendations to address the identified limitations. Your expertise, multidisciplinary vision, and valuable contributions have allowed for the creation of this document, including perspectives from different areas of knowledge.

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CONTEXT

The objective of the National Health System is to contribute to improving the health and quality of life of the population, by carrying out actions aimed at preserving, protecting, and promoting population health, preventing diseases, and promoting research and innovation as drivers of development, social well-being, and progress of the healthcare system. Thus, the public healthcare system provides universal health care centered on the patient, under conditions of maximum safety and effectivenes possible.[1,2] To fulfill this objective, it is necessary to **guarantee equity in access to healthcare in all territories**, in order to achieve maximum health for the entire population using the available resources, while **maintaining the sustainability of the National Health System over time, through the search for balance between health outcomes, social and financial aspects**.[3]

Achieving this balance is essential, as we are facing a reality in which healthcare resources are limited and pharmaceutical expenditure and healthcare demand are constantly increasing, due to, among other causes, the aging of the population, the rising prevalence of chronic diseases, polypharmacy, greater access to information and patient involvement in decision-making, and the growing innovation in healthcare technologies. All of this contributes to putting the sustainability of healthcare systems at risk. Therefore, the **optimization and personalization of clinical approaches, as well as the sustainability of healthcare systems**, are considered fundamental aspects in both national agendas and the European Union, which **seek to ensure the quality, effectiveness, and efficiency of healthcare systems** within the possibilities of public budgets.[4]

In this sense, Personalized Precision Medicine, as a holistic health approach, can contribute to the optimization and increased value of healthcare through the prevention and early detection of diseases, patient stratification, early implementation of the most effective and safe treatment based on individual characteristics, drug repurposing, etc.[4] While it is true that health benefits for an individual patient do not automatically translate into substantial added value for the healthcare system and society, **Personalized Precision Medicine offers the opportunity to improve health outcomes and avoid unnecessary long-term expenses**, **contributing to minimizing inefficiencies and biases** derived from medicine based on common objectives for the majority of the population, and therefore, contributes to the sustainability of healthcare systems. In fact, many European countries and regions in Spain

are seeking to implement Personalized Precision Medicine in clinical practice and innovation through various plans, strategies, and infrastructures, with the **aim of achieving more efficient and sustainable healthcare systems.**

Additionally, given that we are in a scenario where resources are limited, for informed decision-making regarding the incorporation of these types of interventions into healthcare systems, it is essential to understand the reality of the value and potential benefit of Personalized Precision Medicine for patients, the system, and society as a whole. Therefore, it is necessary to generate evidence through, for example, the design of clinical trials and the use of surrogate markers, as well as to carry out Health Technology Assessments based on the concepts of efficiency and opportunity cost.[5]

However, there are still challenges and limitations to face in order to demonstrate the contribution of Personalized Precision Medicine to the optimization of resources and health outcomes, such as the absence of evaluation of the impact of investments in the healthcare system by an independent agency or measurement of health outcomes, and therefore, demonstrating its contribution to the sustainability and efficiency of healthcare systems.

The Roche Institute Foundation works to help anticipate the future, accelerate changes, and bring the medicine of the future to the present, through the generation and dissemination of knowledge in Personalized Precision Medicine and Digital Health, thus collaborating in the development of an innovative and sustainable healthcare system.[6] In recent years, the Roche Institute Foundation has not only been a reference in terms of dissemination of this discipline but has also shown its commitment to promoting and implementing Personalized Precision Medicine in the healthcare system through the development of documents to promote public debate, favoring communication among all stakeholders. Based on this commitment and the raised context, the following document is presented on the value of Personalized Precision Medicine in the sustainability and efficiency of the healthcare system of the future.

OBJECTIVES

The main objective of the report is to hightlight and value the contribution of Personalized Precision Medicine to the sustainability and efficiency of the healthcare system.

For this, the following steps are proposed:

- Identifying:
  - The necessary elements for the sustainability and efficiency of the healthcare system.
  - The areas of application of Personalized Precision Medicine in which it would add value in terms of contributing to the sustainability and efficiency of the healthcare system.
  - The potential barriers that the system will face in relation to a sustainable and efficient application of Personalized Precision Medicine.
- Issuing recommendations and proposals by the authors to contribute to the sustainability and efficiency of the healthcare system through the implementation of Personalized Precision Medicine.
- Making visible specific examples that demonstrate the efficiency and effectiveness of Personalized Precision Medicine.

METHODOLOGY

For the development of this document, a multidisciplinary working group was assembled, and it was approached with a widely participative methodology, in line with the nature of Personalized Precision Medicine, in which different professionals and areas of knowledge play a relevant role.

For this purpose, it was established a panel of 14 experts with wide experience in different areas related to Personalized Precision Medicine, under the coordination of Dr. Enrique de Álava, who combines extensive knowledge in Personalized Precision Medicine with great experience in planning.

Figure 1. Professional profiles involved in the development of the document.

The document was carried out in three work phases:

Phase 1: Situation analysis

In phase 1, a situational analysis was performes through a literature review to identife key aspects and successful examples where the application of Personalized Precision Medicine contributed to improving the sustainability and efficiency of the healthcare system, as well as identifying the barriers and limitations that need to be addressed.

Following validation by the coordinator, individual interviews were conducted with all the experts, through which they were able to provide their insights on the key aspects of the contribution of Personalized Precision Medicine to the sustainability and efficiency of the healthcare system, and to make recommendations for addressing the barriers and limitations identified.

Phase 2: Sharing and consensus

Following the individual interviews, during phase 2, two workshops were held with the working group to reach a consensus on the key aspects identified in the previous phase and the contents of the report. The workshops also addressed recommendations to tackle the barriers and limitations to the sustainable and efficient implementation of Personalized Precision Medicine in the healthcare system.

Phase 3: Report development

In phase 3, the report "The Value of Personalized Precision Medicine in the Sustainability and Efficiency of the Healthcare System" was developed, which, after the review of the structure and contents and subsequent validation by the coordinator, was also validated by the group of experts.

NECESSARY ELEMENTS FOR THE SUSTAINABILITY AND EFFICIENCY

The National Health System must offer the most efficient solutions that provide the most value for the entire population in an equitable manner across all territories, ensuring its own sustainability over time. To achieve this**, a balance must be struck between health outcomes, financial and social aspects**. In this way, quality can be guaranteed not only in terms of accessibility, but also in terms of appropriate waiting times, healthcare system digitization, and the well-being of healthcare professionals, all of this focused on contributing to improving the quality of life, health, and people's satisfaction.[1,7]

In this regard, a series of necessary elements have been identified to ensure the sustainability and efficiency of the future healthcare system: the orientation of the healthcare system, healthcare resources, research, training, digital transformation, healthcare system planning, and the regulatory framework and ethical control mechanisms.

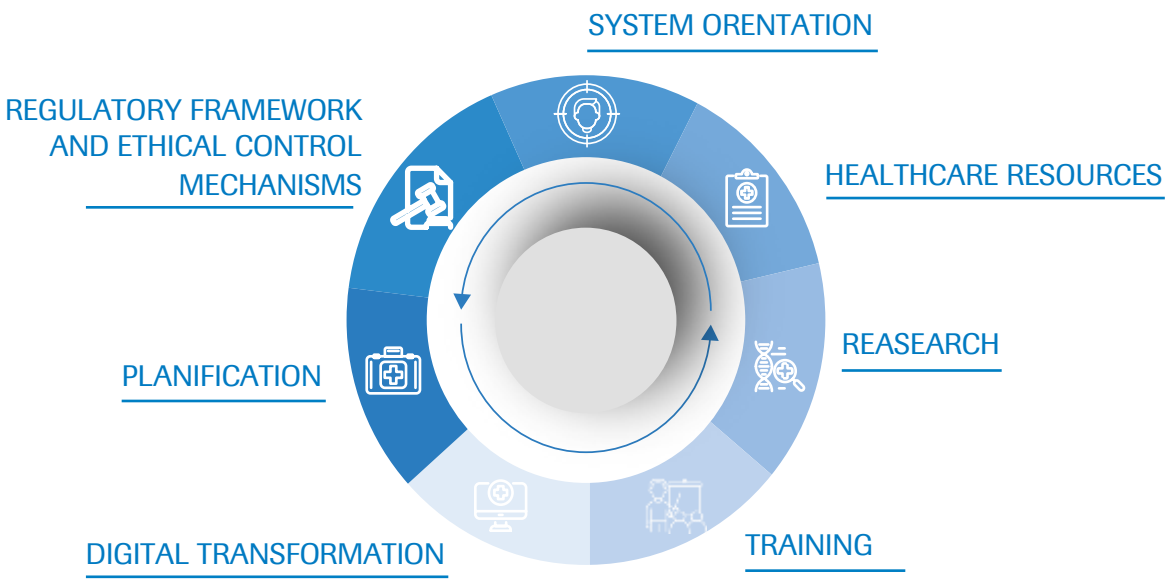


Figure 2. Necessary elements for the sustainability and efficiency of the healthcare system.

- **System orientation.** Healthcare systems should facilitate all aspects related to health and well-being, **promoting disease prevention** through integrated care in hospitals, primary care, and social and healthcare services. To achieve this, it is essential to **ensure care continuity** to minimize inefficiencies, taking into account the available healthcare technologies and resources. Furthermore, in line with its goal of improving

people's health and quality of life, health care should be **centered on the needs of patients**, who increasingly have greater access to information and participation in decision-making.

- **Healthcare resources.** The healthcare system must have the **material resources** (supplies, infrastructure, and facilities),[8] **financial resources**, **human resources** (including healthcare and administrative support staff), and **IT resources** (both hardware and software, including elements necessary for Digital Health) that allow, at a minimum, the provision of healthcare services included in the common services portfolio of the National Health System.[9]

- **Research.** Research, whether pharmacological, biomedical, process-oriented, or management-related, serves as a **driver for the sustainability** of healthcare systems. This is the case not only because it contributes to generating knowledge about diseases, developing technologies and innovations, and translating and applying its results to clinical practice, but also because it allows healthcare systems to learn from their own processes to optimize them and be more efficient, as in the case of networked research.

- **Training.** Adequate training of all stakeholders in the system (managers, healthcare professionals, technicians, administrative staff, and users) is necessary to raise awareness about the **correct use and consumption of healthcare resources**, as well as for the efficient and sustainable **implementation of technological innovations** and Personalized Precision Medicine in routine clinical practice.

- **Digital transformation.** The digital transformation of healthcare systems makes possible to **optimize, automate, and avoid duplications** in numerous processes, and it can also reduce the consumption of healthcare resources, contributing to their efficiency. This is achieved through access to and exchange of data and information facilitated by digitization and the availability of an integrated electronic health record, the establishment of telemedicine systems and clinical decision support, and the development of participatory health.

- **Healthcare system planification.** A proper planning is essential to ensure the efficiency and sustainability of the healthcare system, where its complexity and the fragmentation of healthcare are increasing. This planning should be carried out rationally, in the medium and long term, with the participation of healthcare

professionals and the citizens, as it is relevant to understand the expenditure that society is willing to asume for the incorporation of healthcare innovations. In this regard, planning **contributes to the sustainability and efficiency of healthcare systems** by allowing the identification of which processes have the most impact in terms of expenditure and health outcomes, which ones represent savings, and which ones generate income for the system (patents, clinical trials, collaboration with industry, etc.), and prioritizing healthcare strategies that have demonstrated value compared to those that do not, according to scientific evidence. To achieve this, the healthcare system **must incorporate the measurement of health outcomes to detect inefficiencies**, **improvement opportunities**, **and strategies that add value**, as well as evaluate healthcare technologies and/or innovations and the investments made. Additionally, system planning should **organize and size the workforce** according to workloads, provide healthcare system staff with appropriate remuneration and working conditions, and allow for a minimum time for care and research. Finally, it is worth mentioning the relevance of public-private collaboration in contributing to the sustainability of the system, as it greatly helps improve the population's access to care, reduce waiting times, or relieve the public healthcare system in terms of reducing the consumption of available resources, among other benefits.[10]

- **Regulatory framework and ethical control mechanisms.** The regulatory framework of the Spanish healthcare system must be **aligned with European regulations and adapted to technological and scientific advances**. Furthermore, to ensure its sustainability and evidence-based practices, the regulations should allow the incorporation of these innovations in clinical practice, guaranteeing the rights of patients, equity, and universal access to care, transparent decision-making based on the best available scientific evidence. On the other hand, it should consider what is established regarding the treatment of citizens' health data and have relevant ethical control mechanisms to ensure the safety and accessibility of this information for legitimate purposes by healthcare professionals, researchers, and authorities

CONTRIBUTION OF PERSONALIZED PRECISION MEDICINE TO THE SUSTAINABILITY AND EFFICIENCY OF THE HEALTHCARE SYSTEM

Personalized Precision Medicine consists of the identification and integration of different types of data such as omics (genomic, epigenomic, etc.), clinical, including anatomopathological, environmental, epidemiological, social and/or economic determinants, using high-performance technologies and Digital Health as key tools, to offer the most effective preventive, prognostic, diagnostic, and therapeutic approaches for each person. This paradigm shift in medicine contributes to the comprehensive approach to health, which also includes social and psychological care, and is applicable at all levels of the healthcare system and areas of health.

Personalized Precision Medicine enables understanding of the differences between individuals with the same process, personalizing their care, and adapting healthcare systems to meet patient's unmet needs. Thus, Personalized Precision Medicine can substantially contribute to improving the health and quality of life of patients with its application in different interventions such as precision diagnosis, disease prevention and health promotion, and the management and monitoring of diseases (acute or chronic), etc.

In this way, while the complete incorporation of Personalized Precision Medicine requires a change in the orientation of the system, the availability of resources, research, and training, proper planning, and the development of a regulatory framework, in the long term, it would imply savings for the healthcare system, contributing to its sustainability and efficiency, due to its potential benefits in terms of:

The **improvement of clinical outcomes** and **quality of life** for patients and their caregivers/family members.

The **improvement of the efficacy, effectiveness and efficiency** of the administrated treatments

The **reduction of toxicity and adverse effects** of medication and the consequence of diseases.

The **reduction of health outcome disparities** that can be achieved with healthcare interventions.

In this sense, a series of **areas of application of Personalized Precision Medicine have been identified in which it would contribute value in terms of sustainability and efficiency of the healthcare system**. Therefore, this section is structured based on these areas in order to delve into them. The identified areas are: Research, Disease Prediction and Prevention, Screening and Precision Diagnosis, Treatment, Follow up and Monitoring, Healthcare Delivery and Management.

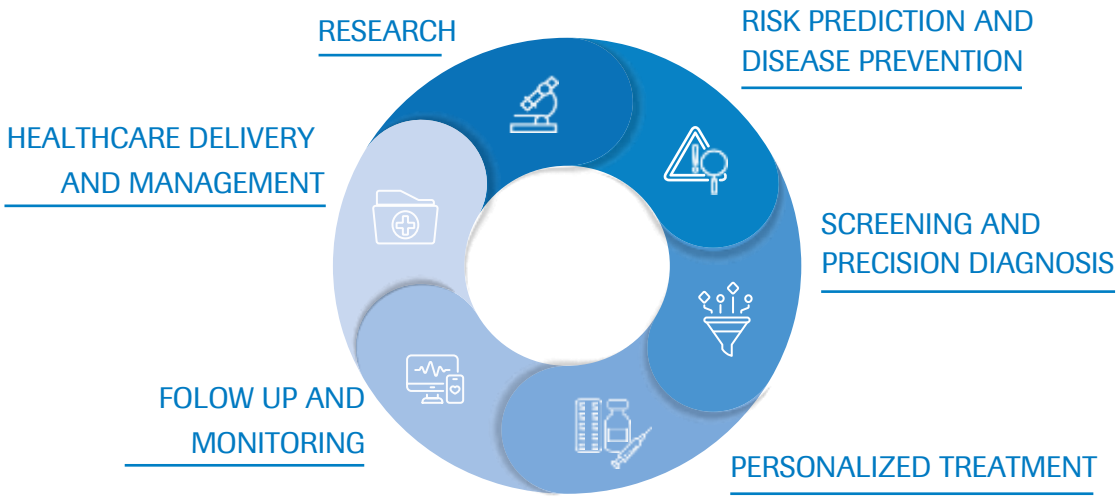
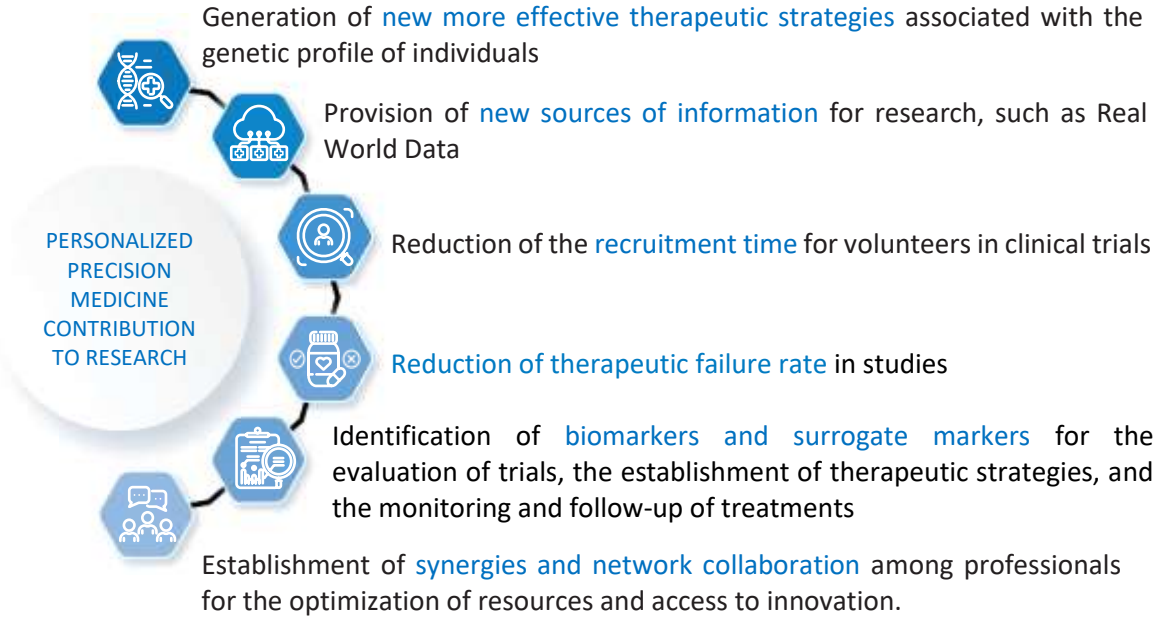


Figure 3. Areas in which Personalized Precision Medicine would contribute to the sustainability and efficiency of the healthcare system.

Research

Personalized Precision Medicine allows **biomedical research**, **particularly in the case of pharmacological research,** to achieve a better understanding of the different **biological mechanisms and molecular bases** that lead to diseases, contributing to the **identification of biomarkers and potential therapeutic targets**. To do this, it relies on high-performance and computational technologies, such as Next-Generation Sequencing (NGS) or Artificial Intelligence, which will favor the optimization of research and innovation in all its stages in the future. In fact, there are different national and international pilot projects aimed at deepening this knowledge to serve as a basis for the development of Personalized Precision Medicine, such as the **Pilot Project of the Medical Genome of Andalusia** for the sequencing and analysis of genomic data to optimize therapeutic decisions, especially in rare diseases[11]; or the **European 1 Million Genomes Project**, which aims to improve accessibility to genomic and clinical data across Europe to enhance research (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine).[12]

With the application of knowledge derived from Personalized Precision Medicine, the door is opened to new research designs and strategies (for more information, see the Anticipating Report on Pharmacological Research in the era of Personalized Precision Medicine) that would allow:[10,13]

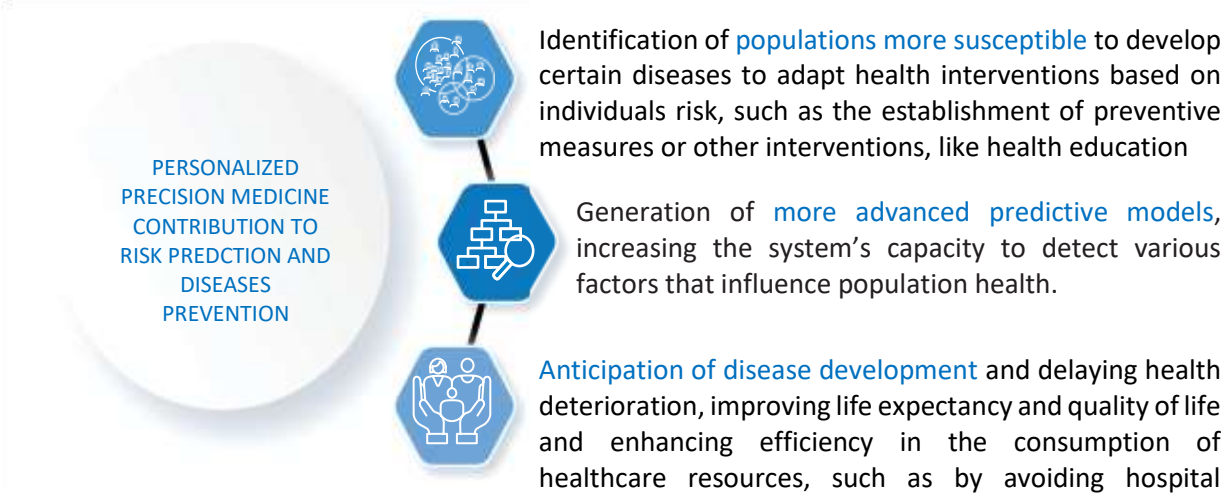


This is relevant because, in this way, it can **contribute to the reduction of costs and times in clinical trials** (both for their development and for the translation of their results into clinical practice[14] increasing their value and providing higher quality results. In this regard, the Carlos III Health Institute is developing the **Infrastructure of Precision Medicine Associated with Science and Technology (IMPaCT)**, whose **strategic axis 3 "Genomic Medicine"** promotes the establishment of a cooperative network, distributed in various nodes for the performance of highly complex genetic studies (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine).[15]

Risk prediction and Diseases prevention

The **prediction of risk and disease prevention** is a key **pillar to ensure the sustainability of the healthcare system**. Therefore, in recent years, thanks to advances in molecular biology, sequencing technologies, and the introduction of digital technologies into medical care, the focus has been on identifying markers that indicate the risk of disease before it manifests, for early disease detection, or to improve the quality of life of patients by limiting or delaying complications.[4]

In this sense, Population-Level Personalized Precision Medicine, known as **Precision Public Health**, thanks to the availability of information related to various health determinants such as lifestyle, genotype, phenotype, etc., would favor **the prediction of disease** development risk and **primary, secondary, and tertiary disease prevention** by allowing:



An example of this is the use of Artificial Intelligence tools that are already being employed in Spanish hospitals for individuals with Chronic Obstructive Pulmonary Disease (COPD) to anticipate potential exacerbations in patients. In this way, the healthcare system is able to anticipate the deterioration of the patients' health status and prevent the need for emergency admissions, thereby improving the quality of life of patients and reducing hospitalizations.[16]

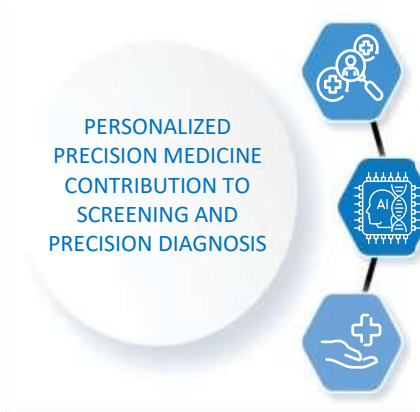
On the other hand, the **IMPaCT initiative**, in its **strategic axis 1 "Predictive Medicine**", includes the **COHORT Program** aimed at identifying the characteristics of the population residing in Spain based on a representative cohort, considering its ethnic variability, geographic diversity, and environmental factors. In this way, the aim is to contribute to the design of predictive models and precision strategies for primary prevention, early diagnosis, and early treatment of diseases.[15] In line with this, the Marqués de Valdecilla Research Institute launched the **"Cohorte Cantabria" project**, in 2021, with the objective of collecting samples and health information from volunteers to gather real-life data from the community (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine).[17]

In fact, the incorporation of genomic information into the risk prediction models developed so far, whether for point mutations, such as the detection of mutations in the *BRCA1* and *BRCA2* genes in individuals predisposed to breast cancer,[18] or for Polygenic Risk Scores (PRS), could

significantly improve their predictive capacity and the stratification of individuals according to disease risk, with the aim of enhancing prevention strategies. In this way, the **integration of Personalized Precision Medicine in prevention could guide clinical decision-making, and the selection or prioritization of treatments for individuals or patient groups,** contributing to improving people's quality of life and the sustainability of the healthcare system.[4]

Screening and Precision diagnosis

Personalized Precision Medicine, alongside omics technologies and the digital transformation of the healthcare system, would allow for the identification of biomarkers for screening, patient stratification, and diagnosis, thereby:



More accuarte selection of patients in whom health interventions are likely to be more effective, meaning they will have a greater relevant additional clinical benefit and fewer complications

Reduction of workload for healthcare professionals by using Artificial Intelligence in the automation of the study of diagnostic and predictive biomarkers and the analysis of medical information, especially medical imaging, thereby optimizing the use of these techniques.

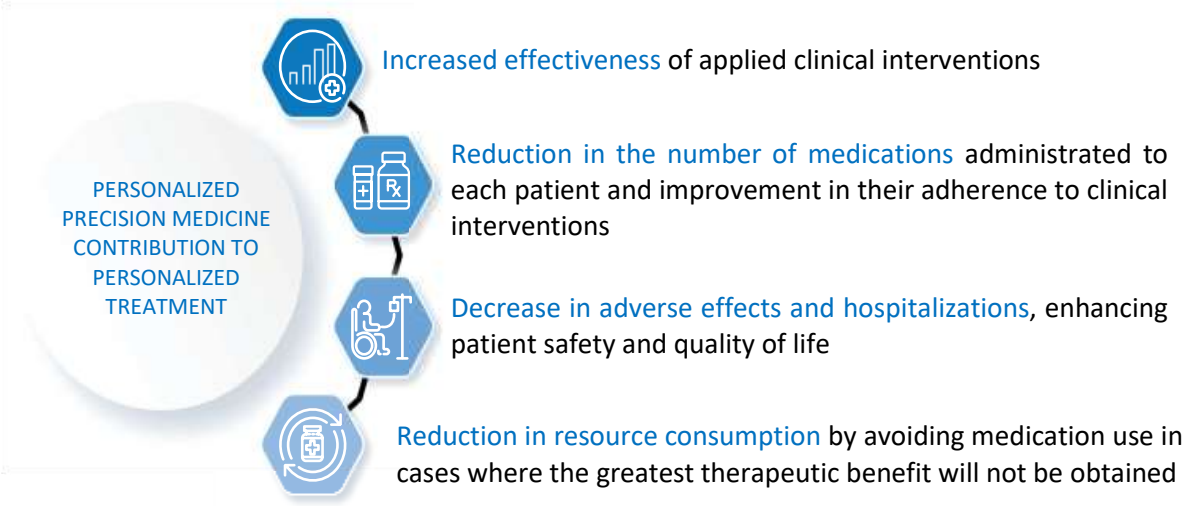
Early establishment of health interventions and/or necessary support measures, minimizing health deterioration. For example, through massive genome sequencing of rare diseases, it is possible to shorten the time to diagnosis.

In this regard, it has been suggested that, thanks to the application of precision screening and diagnostic techniques, it not only **reduces the direct costs of the disease but also those related to long-term complications due to early treatment initiation**.[14,19] For example, in a study on the clinical and economic impact of ALK rearrangement testing, it was observed that non-small cell lung cancer screening is a cost-effective strategy, meaning that the benefits outweigh the intervention costs. Additionally, high-throughput technologies such as Next Generation Sequencing (NGS) can be employed for non-small cell lung cancer screening in reference centers efficiently, as concluded by another study conducted in Spain (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine).[20]

Personalized treatment

Incorporating Personalized Precision Medicine into the healthcare system would help **identife patient characteristics that incluence their response to medications,** as is the case

with certain **genetic variants**. In this way, it would be possible to integrate information about **pharmacogenetic and pharmacogenomic profiles** with **clinical information**, **personalize treatment** based on individual variability in pharmacological response, and thereby: [14]



In this regard, there are numerous examples of how personalized treatment provides substantial benefit compared to non-specific therapy. For example, in the field of oncology, the personalization of treatments is not limited solely to the characteristics of each patient, but it is possible to design personalized treatments based on the genetic profile of the tumor, improving their outcomes.[21] In fact, the Ministry of Health has published, in January 2024, the first proposal for a common catalog of genetic tests for the identification of biomarkers associated with specific treatment, which will be included in the Basic Services Portfolio.[22]

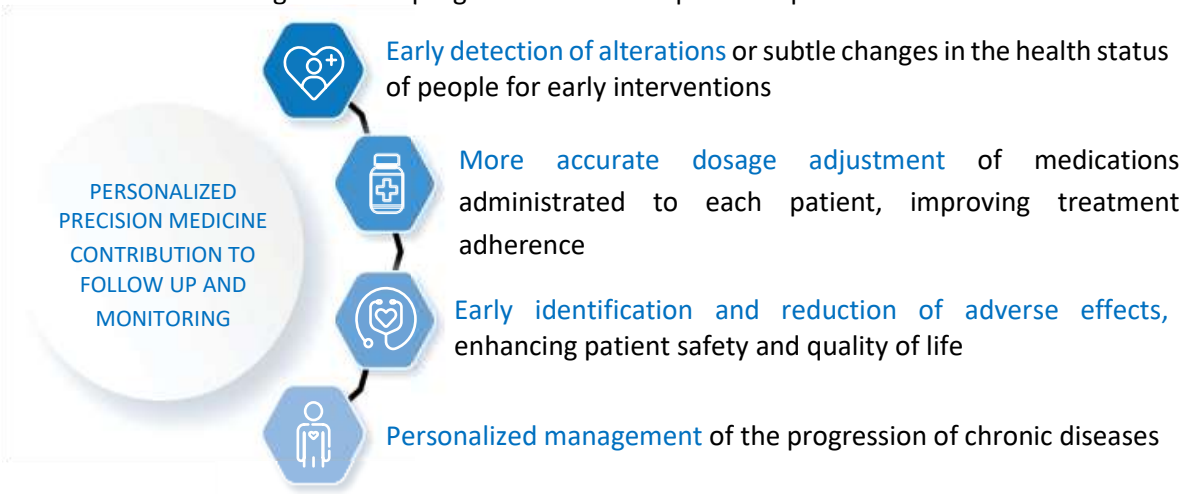
On the other hand, the study of pharmacogenetic variations and their integration with individuals' clinical information would significantly contribute to the therapeutic decision-making process, as seen with the application of **the 5SPM (5 Step Precision Medicine Model)** in various medical specialties in Castilla y León. This model is designed for the personalization of treatment based on the pharmacogenomic profile of patients who experience therapeutic failure or serious adverse effects. The model simultaneously evaluates the effects of pharmacogenetic interactions in the context of each patient's polytherapy (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine)).[14,23]

Thus, while personalized treatments may initially require an initial investment, thanks to the achievement of better health outcomes, increased treatment adherence, reduced hospitalizations due to adverse effects, decreased relapses due to therapeutic failure, etc., in

the long term, it would imply a **potentially more efficient use of healthcare resources and therefore result in cost savings for the system**.[14]

Follow up and Monitoring

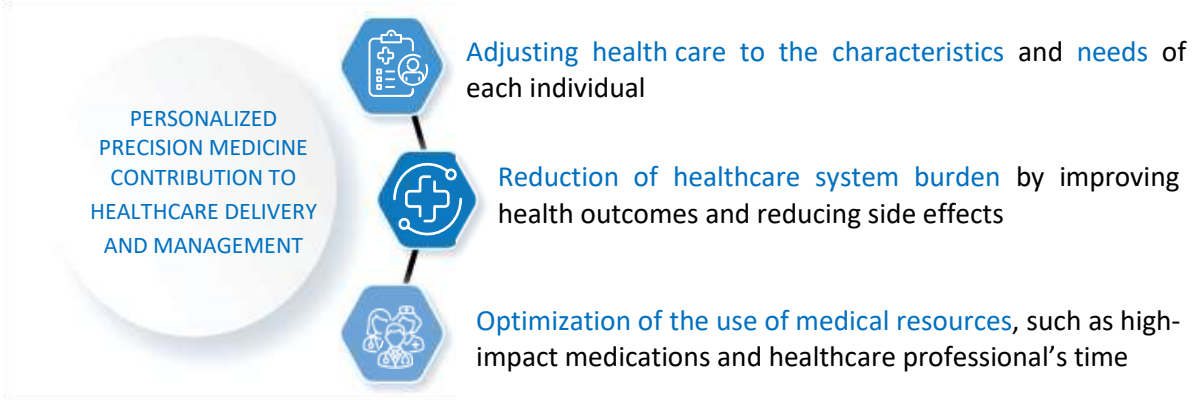
The application of Personalized Precision Medicine, hand in hand with omics sciences (genomics, proteomics, metabolomics, etc.), provides knowledge about **biomarkers and surrogate markers linked to the progression or prognosis of diseases**. This information is essential for the proper follow up and monitoring of each patient, enabling the early detection of changes in their progression and anticipation of potential health deteriorations.



An example is the use of liquid biopsy for cancer follow up and monitoring, which is not only a simple and minimally invasive procedure, but it is also cost-effective and highly efficient.[24] Furthermore, thanks to Digital Health tools and telemedicine, Personalized Precision Medicine would contribute to the remote follow up and monitoring of patients, reducing unnecessary hospitalizations or healthcare consultations and preventing the inefficient consumption of resources. An example of this is the results of a study conducted by John Hopkins University on the use of participatory health devices (wearables) for monitoring patients with chronic diseases. These devices are beginning to be used in different situations as it has been observed that their use in clinical practice would allow for treatment adjustments based on their lifestyle, using measurements of heart rate, respiratory rate, temperature, physical activity, etc., contributing to improving their quality of life.[25]

Healthcare delivery and management

With its enhanced understanding of diseases and patient needs, Personalized Precision Medicine can help adapt **healthcare delivery and management to a more integrated and holistic vision of health**, facilitating the reorganization of resource use.



In this regard, numerous strategies are already available both at the national level in different countries and at the regional level, for the proper implementation of Personalized Precision Medicine (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine), ensuring accessibility to innovation, appropriate response time, and the quality of healthcare.

For example, by establishing official reference centers for centralized genetic diagnosis contributes to concentrate resources and allows for more efficient processes, due to the greater expertise of professionals.[26]

Regarding the compilation of information in different areas such as cardiology, the promotion of public-private collaborations can contribute to the transition from acute care to long-term risk prevention and management, as well as to improving cardiovascular health across the entire Spanish population.[27]

On the other hand, the creation and implementation of tools that allow the integration of clinical, genomic, imaging, lifestyle habits, or previous adverse effects data into the Electronic Health Record, and the provision of tools that enable data exploitation and the integration of omics data with clinical data, would contribute to optimizing the use of information.[26] In fact, the **strategic axis 2 "Data Science" of the IMPaCT initiative** includes the **DATA Program**, aimed at the development and validation of an environment for the integration and joint analysis of clinical, molecular, and genetic data, for its secondary use (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine).[15]

All of this, **in addition to improving patients' perception and degree of satisfaction, would bring great value and efficiency to the system**. To achieve this, the establishment of health policies and strategies is required to analyze the planning and coordination among all stakeholders in the system, for the more efficient management of healthcare resources and to ensure the inclusion of services supported by the best available scientific evidence. This could be promoted, for example, through the definition of the common services portfolio of the National Health System by the Commission of Benefits, Assurance, and Financing, under the Interterritorial Council of the National Health System, or the provision of Integrated Care Protocols that define the role and coordination of all professionals and care levels involved in a specific disease or process.

In this regard, it is worth noting the **HEcoPerMed project**, which is being developed at the European level to generate robust evidence on the value that Personalized Precision Medicine brings to society, as well as the long-term effectiveness and efficiency of different Personalized Precision Medicine interventions, in order to serve as a guide for decision-makers for their incorporation into the healthcare system (for more information, see ANNEX I: Initiatives for the implementation of Personalized Precision Medicine)[28] .

PERSONALIZED PRECISION MEDICINE EVALUATION

The **economic evaluation of healthcare technologies** has become a fundamental tool for **resource allocation** by healthcare managers in Europe in recent years, as it provides information about the economic value of these technologies. This information is highly relevant for **decision-making related to the efficient incorporation of disruptive innovation in healthcare** into healthcare systems, in order to promote equity and sustainability. For this purpose, it is necessary for these evaluations to be carried out with a comprehensive approach that addresses both health outcomes and costs, using the best available evidence. However, there are currently no specific guidelines for the **evaluation of Personalized Precision Medicine** that take into account its complexity.

In this sense, **measuring health outcomes** is essential **to determine which therapeutic, technological, or management innovations truly constitute improvements for the healthcare system in terms of efficiency**.[31] Additionally, the correlation between these health outcomes and resource consumption when using different therapeutic alternatives is a key aspect in determining efficiency and its contribution to the medium and long-term sustainability of the healthcare system.[32]

Traditionally, this information on clinical outcomes is obtained, whenever possible, from **randomized clinical trials aimed at assessing the effectiveness and safety of healthcare interventions**. In randomized clinical trials, the goal is to **generate evidence on clinically significant variables**, parameters that reflect the patient's health status in terms of functional status or even survival. These variables are currently used as criteria in therapy assessment; however, their study requires a large sample size and a long follow-up period.[33]

In the context of **Personalized Precision Medicine**, clinical trials **populations** may be very small due to the stratification of the study population or to novel trial designs, such as n-of-1 trials, which involved a single individual. These new approaches, as they do not adhere to the classic design of randomized clinical trials, can, in some cases, **hinder the conduct of comparative studies of effectiveness**, **the generation of scientific evidence, and the evaluation of therapeutic interventions or strategies**. Nevertheless, it is still necessary to generate scientific evidence on clinical outcomes, as well as to perform clinical and analytical validation of Personalized Precision Medicine applications

to demonstrate their safety, efficacy, precision, reliability, and the consistency of the results they provide

In fact, the **health information used in health technology assessments generally is limited to clinical outcomes**, although it should also take into consideration the **improvement of quality of life, unmet medical needs, disease severity, or the existence of therapeutic alternatives**, among others. Additionally, while this is not an exclusive aspect of Personalized Precision Medicine, in some cases, it is not possible to know the full value that healthcare interventions or technologies provide throughout their entire useful life. To demonstrate the magnitude and duration of health benefits, other biomarkers and surrogate markers can be used in addition to clinically significant variables. A **surrogate marker** is an assessment criterion that uses clinical markers to indirectly measure a patient's health status or survival. For example, a surrogate marker for bone fracture (which would be the clinically significant variable) could be bone mineral density, or in the case of cancer, progression-free survival is the surrogate marker for overall survival. It is important to note that in order to use these surrogate markers, it is necessary to demonstrate beforehand that they are closely related to the clinically significant variable. Once validated, they can be used in clinical trials, resulting in reduced time and the number of volunteers needed for the trials, improving their efficiency, and therefore accelerating patient access to innovation.[33]

Furthermore, in order to fully reflect the clinical value provided by new treatments, it is important to consider that **health outcomes go beyond what occurs in controlled clinical trials conducted in "ideal" laboratory conditions**. Therefore, m**easuring health outcomes in routine clinical practice** is important to understand how these new treatments work and to make the most appropriate therapeutic decisions. In this sense, surrogate markers could also be used in real-world conditions to understand the benefits of different therapies, particularly Personalized Precision Medicine, and to implement patient-centered medicine that is beneficial for society and the healthcare system. Therefore, it is essential to **reconsider the way technology evaluations are conducted to determine the long-term benefits, especially in the case of Personalized Precision Medicine**.

On the other hand, the **costs** used in these evaluations generally are limited to direct healthcare costs. However, in the current context of limited resources, it is important to **understand the real economic impact that the incorporation of new healthcare technologies** will have on the healthcare system. To achieve this, other costs, such as **indirect healthcare costs or non-healthcare costs, both direct and indirect**, should also be taken into account. In

this way, social costs could be considered (for example, in terms of loss of labor productivity or the cost of informal care that patients and their families must bear) and the contribution of Personalized Precision Medicine to optimizing resource consumption (for example, by reducing the prescription of treatments for patients who will not benefit from them or by preventing toxicities and side effects).[32]

Additionally, it is worth mentioning that, generally, **not all stakeholders are involved in healthcare technology assessments, such as patients, society in general, healthcare professionals, or the pharmaceutical industry**. However, these stakeholders could contribute to **measuring health outcomes in the healthcare system and identifying unmet needs** to direct resources. Therefore, incorporating these perspectives in the future of healthcare technology assessments will help **complete the information supporting decision-making for the incorporation of innovations** that contribute to improving population health, healthcare system efficiency, and sustainability.

LIMITATIONS TO CONTRIBUTE TO THE SUSTAINABILITY AND EFFICIENCY OF THE HEALTHCARE SYSTEM THROUGH PERSONALIZED PRECISION MEDICINE

As indicated throughout the report, Personalized Precision Medicine would contribute to achieving the sustainability and efficiency of the healthcare system. Therefore, any barriers that hinder its proper implementation will also represent a limitation in achieving the sustainability and efficiency of the system. The following are the limitations identified by the group of experts, grouped according to the elements necessary for the sustainability and efficiency of the healthcare system: the orientation of the healthcare system, healthcare resources, research, training, digital transformation, healthcare system planning, and the regulatory and ethical framework.

Limitations related to the orientation of the healthcare system

- **Limited optimization and adaptation of healthcare processes** for the prevention and management of chronic diseases due to the increase in chronic conditions or the aging of the population, which contribute to the increased burden on the healthcare system and hinder its long-term sustainability.
- Decentralization and insuffcient coordination among Regions can lead to inefficiencies or inequities in the provision of healthcare to patients, and can make difficult the efficient implementation of Personalized Precision Medicine in the healthcare system. For example, centers without access to genetic testing may not be able to offer certain therapies to patients based on their genetic profile.
- **Inadequate coordination and integration between primary care and hospital care levels**, affecting the continuity of care and the optimal management of resources. This is particularly relevant in Personalized Precision Medicine, which often requires a coordinated approach in data collection and analysis for its implementation. Additionally, information about the availability of tools and applications related to Personalized Precision Medicine does not reach healthcare professionals, potentially hindering the adoption of new practices.

› **Limited involvement of the population, especially patients, in decision-making regarding the organization and management of the healthcare system**. This involvement is essential to take into account the actual needs and priorities of the population in guiding and shaping the healthcare system.

Limitations related to healthcare resources

› **Limited initial investment for the implementation of new healthcare technologies** and **treatments** in Personalized Precision Medicine, such as genetic analysis, is decreasing as sequencing technologies advance.[9] Additionally, **financial stability is required within the healthcare system**, which affects its ability to guarantee and maintain the essential material, technological, and human resources necessary to meet the population's needs

› **Insufficiently trained personnel in Personalized Precision Medicine and the difficulty in incorporating new professional profiles required in multidisciplinary medical care teams**, such as geneticists, molecular biologists, and biomedical informatics specialists, may limit the proper development and effective implementation of these approaches in the healthcare system. Furthermore, the irregular incorporation of these professional profiles into the staff in the Regions contributes to the emergence of inequalities in comprehensive and personalized patient care.

› **Outdated infrastructure and equipment** in some areas of the healthcare system hinder, and at times can prevent, the incorporation of emerging therapies. Specifically, for Personalized Precision Medicine to be integrated sustainably and efficiently, it requires specialized infrastructure and equipment. Currently, the healthcare system is not generally equipped to perform tasks such as the extraction and analysis of genetic samples from the population, and the collection and analysis of large amounts of data for patient stratification or identification for disease diagnosis and treatment.

› **Lack of systematic and widespread health outcomes measurement in healthcare processes or management to identife inefficiencies**. Having this information could help identify inefficient processes or strategies, or suboptimal resource allocation, allowing the responsible agents in healthcare management to make decisions accordingly.

Limitations related to research

› **Lack of optimal and validated indicators for measuring clinical outcomes** in research in the field of Personalized Precision Medicine is a significant challenge. In many cases, clinical trial endpoints or objectives are used that are not always applicable for evaluating new therapies or are not ideal. In fact, the use of certain endpoints in measuring clinical outcomes can lead to delays in generating evidence about the outcomes of specific interventions in chronic processes.

› **Lack of clinical research investigator profiles**, as well as the means and resources to attract and retain the talent of professionals who wish to dedicate themselves to research, such as the establishment of a regulated research career in biomedicine.

› **Insufficient collaboration between professionals from different fields or between public and private research institutions or centers** hinders the sharing of knowledge, technologies, and resources for drug discovery or the development of clinical trials, among other challenges..

Limitations related to training

› **Limited training opportunities on aspects related to Personalized Precision Medicine** aimed at healthcare professionals and managers, both at the university level and in specialized healthcare training, pose a significant challenge. For example, the interpretation of genetic test results is highly complex and requires specific training for the professionals responsible for analyzing the samples and reporting the results, as well as for the managers who must organize the staff and processes of the centers.

› **Lack of training and acquisition of competencies** by healthcare system professionals at various levels, as well as their **certification and periodic recertification** in the application of Personalized Precision Medicine to ensure its efficient use.

› **Insufficient training and awareness among all stakeholders** in the healthcare system regarding the relevance of optimal use of available resources, the evaluation of healthcare technologies, and the measurement of real-life health outcomes. The lack of involvement in this regard results in resistance to change, which hinders the adoption of Personalized Precision Medicine applications in the healthcare system and, consequently, prevents patients from benefiting from them.

Limitations related to digital transformation

- **Lack of integration of genetic information with other data generated by the healthcare system and real-world data** in a widespread manner within the healthcare system is a significant barrier. This prevents the implementation of Personalized Precision Medicine strategies that have proven effective in clinical practice, such as the application of pharmacogenetics for tailoring treatments based on patients' genetic profiles.[14,34]

- The **limited implementation of digital technologies, such as telemedicine**, is hindered by the restricted availability of Information and Communication Technologies (ICT), especially in rural areas, and by the fact that remote assistance is not considered in the work schedule of healthcare professionals. Advances in digitalization, such as digital pathology, could, for example, enable patient samples to be analyzed by pathologists not located in the same city.

- **Resistance to change and unfamiliarity with new technologies** can hinder the adoption of digital approaches in Personalized Precision Medicine, such as continuous health monitoring for early detection of health alterations.

- **Lack of systems for the evaluation and validation of new technologies and digital tools**, such as Artificial Intelligence, for their application in the healthcare system, both for clinical practice and healthcare management applications.

- **Limited adoption of data standardization criteria that facilitate data exchange and interoperability between information systems of Regions**, **provinces, or hospital centers**, as well as between different care levels, **public and private systems**, or **between the healthcare and social systems**, leads to duplications and inefficient resource management.[16] Esto da lugar a duplicidades y una gestión ineficiente de los recursos como, por ejemplo, cuando un profesional sanitario no tiene acceso a la historia clínica electrónica de un paciente procedente de otra comunidad y debe recabar la información de nuevo.

Limitations related to the healthcare system planning

- **Lack of specific budget allocation for the development of Personalized Precision Medicine** is a significant challenge. Additionally, there is high geographic variability in investment in Personalized Precision Medicine due to differences in resource

availability among the Regions, resulting in heterogeneous development across the healthcare system, leading to territorial inequity.[9]

- **Lack of coordination for the implementation of Personalized Precision Medicine and the integration of different initiatives being designed and promoted in the Regions** results in an imbalance regarding the innovations, technologies, and/or techniques of Personalized Precision Medicine to which patients have access.

- **Absence of health outcome measurement and the lack of a culture of evaluating healthcare technologies** means that systematic evaluations are not consistently conducted within the healthcare system. The absence of these evaluation results can hinder the identification of areas for improvement and evidence-based decision-making in healthcare planning. Additionally, all stakeholders in the system, decision-makers, managers, healthcare professionals, and the general population, should participate in these processes. Specifically, the participation of the general population would allow prioritization based on societal needs.

- **Absence of an independent body for evaluating Personalized Precision Medicine healthcare technologies**, both for their incorporation into the healthcare system and those used in routine practice, is a significant challenge.

- **Delay in the approval and access to new healthcare technologies** in our country. For example, approximately 619 days pass from the authorization of a new drug in Europe until it reaches the Spanish healthcare system, impacting the quality of life of patients due to its late implementation in clinical practice.[35] But this not only affects medications, it is also a reality in other areas, such as the digitization of the healthcare system. For instance, the adoption and access to Clinical Decision Support Systems for Artificial Intelligence-based diagnostic tools can be delayed by rigorous regulatory processes and safety and efficacy evaluations necessary for their approval.

- **Short-term vision in planning** does not allow the healthcare system to anticipate the future needs of the population, allocate resources correctly, and therefore implement Personalized Precision Medicine sustainably and efficiently in the long term.

- **Limited availability of management profiles equipped for the correct implementation of certain Personalized Precision Medicine strategies**, which may be of a high level of complexity in terms of healthcare planning. For example,

in the stratification of the population into patient profiles, it is necessary to have and anticipate the necessary human and infrastructural resources for the proper collection and analysis of information. Decision-makers in the healthcare system must be aware of these needs in order to allocate these resources effectively.

Limitations related to regulatory framework and ethical control mechanisms

- **Delay in adapting the regulatory and legislative framework to the technological and research developments** inevitably leads to a delay in clinical application and technological advancements. An example of this is the use and application of Artificial Intelligence tools in healthcare, which began development in the 1970s. However, it wasn't until 2021 when the European Commission proposed to develop the regulatory framework for the creation of an Artificial Intelligence Law.[36]
- **Complexity of the regulations regarding health data treatment generates legal uncertainty** and, consequently, hinders the agile sharing of data between institutions. In addition, there is a need to align the Spanish national framework related to regulation and governance with the standards, guidelines, and processes for data storage, collection, analysis, and management being developed at the European level.
- It is necessary to **align the Spanish national framework** related to data use regulation and governance with the new standards and processes established at the **European level.**
- **Absence of updated governance regulations for the management of individuals' genetic data** is crucial due to the ethical implications of using genetic data, as they provide sensitive and relevant clinical information about the patient and their family members.
- **Lack of equity in access to Personalized Precision Medicine** is not only at a national level but also within Regions, as discussed in previous sections.
- The **ethical implications of resource prioritization in a limited resource environment**. At this point, it is important to consider that, when deciding to implement a particular strategy in the healthcare system, resources must be allocated for its proper incorporation. However, the opportunity cost is behind every decision, and in this

context, the decision to allocate resources to an intervention, pathology, or healthcare area implies that resources are not allocated to others.

RECOMMENDATIONS TO CONTRIBUTE TO THE SUSTAINABILITY AND EFFICIENCY OF THE HEALTHCARE SYSTEM TRHOUGH PERSONALIZED PRECISION MEDICINE

In order to address the previously identified limitations in the healthcare system, a set of recommendations is proposed to achieve a sustainable and efficient system through the implementation of Personalized Precision Medicine. It is important to consider that one or more of these recommendations may provide a solution to one or several limitations. The recommendations are presented below, following the framework of the necessary elements for the sustainability and efficiency of the future healthcare system: the orientation of the healthcare system, healthcare resources, research, education, digital transformation, healthcare system planning, and the regulatory and ethical framework.

Recommendations for the orientation of the healthcare system

- Reach a **Healthcare Pact for the sustainability of the National Health System** that provides stability, facilitates the coordination of the implementation of Personalized Precision Medicine, and ensures equity in resource planning.[1]
- Promote **integrated care models** that improve continuity of care and coordination across different levels of care, define the specific functions of each involved party, and adapt to the characteristics and needs of the population, thereby improving efficiency and quality of care.
- **Allocate investments and resources in primary care and necessary prevention programs** to address health needs in the early stages and reduce the burden on hospitals**.**
- **Implement collaborative networks in the healthcare system to optimize resource coordination and healthcare delivery**. For example, by defining reference nodes for conducting genetic tests to which patient samples, images, or medical history information can be sent without the need for patients to trave.
- **Define protocols and procedures for the consistent implementation of Personalized Precision Medicine within the healthcare system.** For instance, with the incorporation of Personalized Precision Medicine-related interventions in the Portfolio of Services

and Benefits of the National Health System, such as the use of biomarkers, protocols and guidelines are needed on how to incorporate these new services into practice.

› **Review care processes to identify inefficiencies** that allow for optimization and, if necessary, redefine the role and functions of healthcare professionals. This will also facilitate the redistribution of tasks for new professional profiles that will need to be incorporated, as well as process automation in line with digital transformation.

› **Promote public-private collaboration** which, when appropriately managed, reduces costs and risks for the public sector while improving public services for citizens [37].

Recommendations for healthcare resources

› **Evaluate and adjust the healthcare system's financing system** to ensure equitable and stable resource allocation over time, allowing coverage of the population's needs, infrastructure and technological equipment updates, and stable incorporation of healthcare professionals.

› **Promote the systematic and widespread measurement of health outcomes or processes** in the healthcare system to identify inefficient processes or strategies, enabling responsible healthcare management agents to make decisions. This will establish mechanisms for the continuous learning of the healthcare system (Learning Healthcare System) to optimize processes and continuously improve quality.

› **Provide the healthcare system with professionals with new profiles** focused on the implementation of Personalized Precision Medicine, **especially geneticists, molecular biologists, and biomedical informaticians**, as well as for the evaluation of health outcomes. In this regard, the **specific functions of each party** involved in healthcare must also be redefined with the incorporation of new profiles and healthcare technologies

Recommendations for reasearch

› **Promote research on validated biomarkers and surrogate markers** for their standardized use in clinical trials and routine practice to measure health outcomes.[34]

- **Use these biomarkers and surrogate markers to launch pilot projects** to demonstrate the value of implementing Personalized Precision Medicine as a way to ensure access for all patients to new therapies.

- **Establish alliances between the public and private sectors and the academic and healthcare fields.** In this way, synergies will be established by sharing knowledge and resources to promote the transfer of scientific developments to clinical practice.[38]

- **Create multidisciplinary translational research teams** of professionals involved in the development and application of new Personalized Precision Medicine healthcare technologies in clinical practice. This way, when an innovative technology has completed the research phases, its implementation in clinical practice will be faster and more efficient thanks to the effective collaboration among these professionals.

- **Strengthen the role of the clinician-researcher** as a key profile in the translation of biomedical advances and developments and the application of Personalized Precision Medicine in clinical practice, by **incorporating categories of statutory research personnel into health services**.

- **Implement a networking system** that allows organizing available research resources, sharing knowledge, and optimizing the research process.[30] For example, these networks could enhance the translation of results obtained through the decentralization of clinical trials.

Recommendations for training

- **Ensure training in concepts related to Personalized Precision Medicine**, such as genetics or biomedical informatics, as it is identified as particularly relevant to enhance training on the interpretation of genetic tests and good practices for the collection and handling of samples. Likewise, it will be crucial to include training on the measurement of efficiency and sustainability for all healthcare professionals at **all levels** (managers, physicians, nursing professionals, technicians, biosanitary students, etc.) and at **all training stages** (undergraduate, specialized health training, continuing education, etc.).[1]

- **Incorporate new professional profiles into the Specialized Health Training system** that are currently not included in the healthcare system (genetics, molecular biology,

biomedical informatics, biomedicine, etc.) to ensure coverage of the health system's need.[8]

› Develop **accreditation and periodic certification systems** for healthcare professionals in Personalized Precision Medicine competencies.

› **Raise awareness about the responsibility for the efficient use of resources and the need to measure health outcomes and evaluate the efficiency of healthcare technologies** among those involved in the healthcare system, including decision-makers, healthcare professionals, and the general population.

› Promote, from early stages**, education and awareness for the general population in health promotion** (for example, on healthy lifestyle habits), but also in new healthcare technologies and innovations, and in the functioning of the healthcare system.[1]

Recommendations for digital transformation

› **Provide the system with the necessary technological, human, and infrastructure** resources for the homogeneous implementation of digital technologies, reducing the digital divide.

› **Develop standardized work protocols and define quality criteria for the development of digital technologies** in the healthcare field. For example, establishing protocols for telemedicine that formalize this activity and define associated dedicated time would facilitate interaction between patients and healthcare professionals, as well as interconsultations among professionals without the need to refer patients, avoiding unnecessary travel and resource consumption.

› **Encourage the dissemination of the advantages and safety of digital transformation** in medical care to healthcare professionals, as well as to system users.

› **Develop training programs to educate healthcare professionals in the use of digital technologies** implemented in the healthcare system, although the **tools and platforms developed** as part of the digital transformation of the system should be **user-friendly** and for the interpretation of information by healthcare professionals.

› **Facilitate access, exchange, and analysis of information** within the healthcare system, advancing in the **interoperability of systems** and the establishment of **data repositories for secondary use**. This will be crucial for the **integration of genetic**

information with other data generated by the healthcare system and with real-world data.

Recommendations for the healthcare system planning

- Establish a **National Commission on Personalized Precision Medicine** that provides the system with specific resources and reinforces the necessary **technological and human infrastructure for healthcare**, contributing to the viability and success of the implementation of Personalized Precision Medicine in the healthcare system.
- **Promote coordination among Regions for the development of Personalized Precision Medicine plans** that guarantee the implementation and equitable access to Personalized Precision Medicine throughout the national territory. For example, by establishing a National Strategy or Plan for Personalized Precision Medicine that allows the integration of the different initiatives being designed in the Regions.
- **Define standardized procedures for the systematic, dynamic, and homogeneous measurement of health outcomes**, in the medium and long term, of healthcare technologies in the healthcare system, and identify the areas or points where the system loses efficiency using real-world data.
- **Create an independent agency for the evaluation of healthcare technologies**, which carries out studies of the contribution to the sustainability and efficiency of Personalized Precision Medicine, including **social and healthcare funder perspective**. To achieve this, the **process of evaluating healthcare technologies in Spain must be optimized** to consider the particularities of Personalized Precision Medicine strategies, as well as the needs and preferences of the population in order to provide information that assists in decision-making and strategic planning for the incorporation of innovations that have a positive impact on the healthcare system
- **Promote medium and long-term planning of the healthcare system for the incorporation of Personalized Precision Medicine in an agile, efficient, and sustainable manner.** For this purpose, strategies such as Horizon scanning can be employed to identify technological innovations that will represent a disruption in the medicine of the future. This will allow for the advance planning and establishment of relevant resources

(technological, human, national, and regional budgetary) to facilitate the efficient integration of innovation

› **Establish channels of communication between healthcare authorities and stakeholders** in the system, such as healthcare professionals and center managers, but especially patients and users, for the **identification and prioritization of strategies and actions within the framework of Personalized Precision Medicine in line with the interests and needs of the entire population.**

› **Establish new reward and financing systems, and implement a value-based financing model** that contributes to improving the predictability, consistency, and transparency of the process, and that supports the present and future solvency of the system. Additionally, reference values should be established to serve as a guide for what constitutes reasonable value for the healthcare system.[41]

Recommendations for regulatory framework and ethical control mechanisms

› **Collaborate in the development of a regulatory framework** that supports a sustainable implementation and development of Personalized Precision Medicine.[38,42]

› Implement **governance measures, facilitate management, and protect data rights** to safeguard the transfer of sensitive information by the patient and the data management by the healthcare professional in line with the provisions of the European Health Data Space.

› **Strengthen practices that protect patient data privacy** and simultaneously facilitate research and continuous improvement of care.

› Advocate for the **incorporation of interventions** related to **Personalized Precision Medicine** in the **Common Basic Portfolio of Healthcare Services of the National Health System** from all levels of decision-making and action, **ensuring equitable access** for the entire population in the different **Regions**, regardless of their place of residence.

› **Promote effective communication and transparency in decision-making** regarding the incorporation of healthcare technologies in the healthcare system.

› **Establish systems for dynamic review and periodic monitoring** of possible updates to the legislation applicable to Personalized Precision Medicine.

GLOSSARY OF TERMS

Biomarkers: Biological substance that can be objectively measured in the body and assessed as an indicator of the normal or pathological biological state, as a response to a therapeutic intervention, or as a future state of disease.

Liquid biopsy: Laboratory test performed on a sample of blood, urine, or other bodily fluid to search for cancer cells in a tumor or small pieces of DNA, RNA, or other molecules that cells release into bodily fluids.

Quality of life: Impact that health has on how a person feels physically, mentally, and emotionally.

Effectiveness: Measure of the capacity of an intervention (e.g., medication administration or surgery) to produce the desired beneficial effect in real conditions of usual clinical practice. It does not have universal application.

Efficacy: Measure of the capacity of an intervention to produce the desired beneficial effect in ideal and controlled conditions, typically in the context of experimental studies such as clinical trials. It is usually established experimentally and has universal validity.

Efficiency: Measure of the economic aspects associated with healthcare interventions and provides information on the allocation of economic resources to a specific healthcare intervention. A healthcare system is considered efficient when it is capable of providing an acceptable healthcare outcome for society with minimal resource utilization.

Randomized clinical trial: Study in which participants are randomly assigned to separate groups to compare different treatments or other interventions.

Equity: Absence of differences in access to healthcare due to social, economic, demographic, or geographic circumstances.

Polygenic Risk Score: Overall measure of a person's genetic risk of developing a disease compared to the general population.

Health Technology Assesment: Systematic process of evaluating the properties, effects, and/or the impact of healthcare technology. It can address both the direct and desired consequences of technologies as well as the indirect and undesired ones. Its main objective is to inform decision-making in healthcare.

Primary prevention: Measures aimed at preventing the onset of a disease or health problem by controlling causal factors and predisposing or conditioning factors

Secondary prevention: Measures intended for the early diagnosis of incipient disease, without clinical manifestations. It involves the search for diseases in seemingly healthy individuals to detect them as early as possible.

Terciary prevention: Activities aimed at improving the quality of life of patients by reducing disability, limiting or delaying complications, and, when possible, restoring function. It also aims to reduce the impact of the disease and its complications through treatment and rehabilitation

Health resources: Each of the elements that make up a healthcare system, encompassing services for patients, available personnel, equipment, materials, programs, units, tangible and intangible assets involved in healthcare activities aimed at a population sector.

Health outcomes: Benefits produced by treatments or healthcare interventions administered in real life. They cover both clinical outcomes (clinical effectiveness) and humanistic outcomes (quality of life, satisfaction level, health status, and patient preferences), economic outcomes (efficiency and budget impact), and healthcare management outcomes (quality of care, service performance, and system performance).

Sustainability: Meeting the needs of the present without compromising the needs of future generations.

Health technologies: Any medication, healthcare product, or medical or surgical procedures, as well as measures for the prevention, diagnosis, or treatment of diseases used in healthcare.

Value: Improvement in patient health outcomes achieved in relation to the cost of a specific intervention

Surrogate marker: Assessment criterion that can indirectly predict or infer the outcome of the main variable, which in some cases may be difficult to obtain due to time or measurement costs. These variables allow conclusions to be drawn about the effect that the treatment has had on the clinical assessment criterion, and they could be used as a substitute for clinically significant variables.

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ANXEX I: INITIATIVES FOR THE IMPLEMENTATION OF PERSONALIZED PRECISION MEDICINE

Nowadays, Personalized Precision Medicine is the focus of a large number of initiatives, strategies, and pilot projects at the European, national, and regional levels that are generating the necessary evidence to justify its incorporation into the healthcare system as an efficient and sustainable tool.

Below are some projects and initiatives identified as relevant in the context of this report.

European level:

- **European 1 Million Genomes.**[12] Initiated in 2018 and coordinated by the European Commission, it aims to facilitate secure access to genomic and clinical data across Europe to enhance research, personalized healthcare, and health policy development. To achieve its objectives, the project was designed in two stages detailing its activities in four dimensions: governance, trust framework, infrastructure, and data.

- **European Rare Disease Network.**[43] In 2022, this online knowledge-sharing platform was launched with the aim of improving the diagnosis and treatment of rare diseases. The network aims to collect Rare Disease Registries so that they are available for consultation and information search in different European countries

- **ERAPerMed Initiative.**[44] Launched in 2018 and coordinated by the Carlos III Health Institute, this initiative, driven by the European Commission, seeks to carry out innovative collaboration projects in Personalized Precision Medicine. Its objective is to align national research strategies, promote excellence in science, strengthen European competitiveness in Personalized Precision Medicine, and foster cooperation between countries.

- **Healthcare and Pharma Economics in Support of the International Consortium for Personalised Medicine (HEcoPerMed) Project.**[28] Initiated in 2019 and coordinated by the Austrian Institute of Technology and funded by the European Union's Horizon 2020 program, it has been the source of three publications:

    - Harmonization and optimization guidelines for economic evaluations in Personalized Precision Medicine:[45] Published in 2021, it establishes the steps

to increase the consistency and quality of economic evaluations of Personalized Precision Medicine. The target population of this study includes those responsible for designing strategies related to Personalized Precision Medicine and the evaluators.

- Study of the net benefit of Personalized Precision Medicine:[46] Published in 2022, it was concluded that Personalized Precision Medicine provides significant progress in people's health, although its high cost will make nec-neccessary to aplly spending control policies in Personalized Precision Medicine interventions.

- Study on the financing and reimbursement of Personalized Precision Medicine:[47] Published in 2022, seeks to review the different models of reimbursement and financing of Personalized Precision Medicine. The study concludes that both public-private collaboration and shared risk agreements could facilitate the development of Personalized Precision Medicine techniques that have demonstrated significant clinical benefit

› **European Cancer Plan.**[48] In 2021, the European Commission published the European Cancer Plan, which is centered around the goal of saving lives through sustainable cancer prevention, improving early cancer detection, ensuring equality in access to cancer diagnosis and treatment, and enhancing the quality of life for cancer patients and survivors.

› **Cancer Mission.**[49] Launched in 2021 by the European Union as part of Horizon Europe, the mission aims to achieve advances in the next decade that will save at least 3 million lives in Europe. It seeks to extend the life expectancy of cancer patients, achieve a higher quality of life, and consolidate mechanisms to prevent or delay the onset of the disease. A better understanding of the factors and mechanisms that cause cancer forms the basis upon which the pillars of the mission are built: prevention, diagnosis, and treatment.

› **Proposal for regulation for the creation of the European Health Data Space.**[50] Published in 2022 by the European Commission. The overall objective is to ensure that individuals in the EU have greater practical control over their electronic health data, encompassing a set of common rules, standards, and practices, as well as infrastructure and a governance framework aimed at providing a coherent, reliable,

and efficient framework for the use of health data in research, innovation, policy-making, and regulation (secondary use of data).

National level:

At the national level, a major initiative and various studies are being carried out to generate the necessary evidence to justify the use of Personalized Precision Medicine:

- **Precision Medicine Infrastructure Associated with Science and Technology (IMPaCT).**[15] Approved in 2020 and coordinated by the Carlos III Health Institute, it encompasses a set of programs designed to serve the R&D system focused on Personalized Precision Medicine, to enhance the generation and transfer of high-quality knowledge in the National Health System, ensuring scientific-technical excellence, equity, and efficiency in the use of available resources. IMPaCT is divided into three axes: Cohort, Data, and Genomics. Axis 1 "Predictive Medicine" addresses the design and establishment of a representative population-based cohort of the resident population in Spain, its ethnic variability, geographical and environmental diversity, with the participation of all the Regions and prospective follow-up. All this with the aim of contributing to the design of precision strategies and predictive models in primary prevention, early diagnosis, and early treatment of major diseases. Axis 2 "Data Science" is aimed at the development and validation of an integrated environment for the joint analysis of clinical, molecular, and genetic data for their coordinated secondary use with strategic axes 1 and 3. Similarly, this axis will generate models that allow for efficient responses to relevant questions for the National Health System, promoting the generation of high-level knowledge based on these approaches. Axis 3 "Genomic Medicine" promotes the establishment of a cooperative infrastructure distributed in various nodes for the conduct of highly complex genetic studies based on research technologies.

- **"5 Step Precision Medicine Model" – 5SPM.**[14] Developed since 2010 in Castilla y León, this is a model for the application of pharmacogenomics in patients in whom therapeutic failure or the development of serious adverse effects is detected in clinical practice. The international innovation model follows a five-step precision medicine protocol, which includes: (1) obtaining clinical, epidemiological, and therapeutic data; (2) analyzing pharmacogenetic interactions based, among others, on the specific pharmacokinetic pathways of the drugs; (3) pharmacogenetic analysis of the genes

chosen in the study; (4) reorienting the pharmacotherapy applied to the patient based on the data obtained in the previous three steps; (5) studying the results and reevaluating the model, checking the evolution of the patients involved.

› **Molecular diagnosis using NGS in patients with non-small cell lung cancer.**[51] A study published in 2023 on the cost-effectiveness of implementing NGS for the diagnosis of patients with advanced non-small cell lung cancer, treatment with targeted therapies, and enrollment in clinical trials. It concludes that the use of NGS in Spanish reference centers for the molecular diagnosis of patients with metastatic non-small cell lung cancer would be a cost-effective strategy compared to the use of single-gene tests. The use of NGS in Spanish reference centers for the molecular diagnosis of patients with metastatic NSCLC would be a cost-effective strategy compared to the use of single-gene tests.

› **Study of the clinical and economic impact of testing for ALK rearrangement in Spain.**[20] Published in 2021, the objective of this study was to determine the clinical and economic impact of testing compared to a hypothetical situation of no screening. The study concluded that the ALK test in patients with advanced non-small cell lung cancer, non-squamous and squamous, who are never-smokers, provides more than 3000 QALYs in Spain over a lifetime horizon. Comparing this gain in health outcomes with the incremental costs, the resulting incremental cost-effectiveness ratio reinforces that the analysis of non-squamous and squamous non-small cell lung cancer in never-smokers is a cost-effective strategy in Spain.

Regional level:

› **Precision Oncology Network in the Community of Madrid.**[52] Project initiated in 2021 in the Region of Madrid with the aim of achieving excellence in Oncology for the patient, the professional, and society, with equity and efficiency in clinical care and access to new treatments and clinical research.

› **Medea Project in Extremadura.**[53] Launched in 2018 by the Extremadura Health Service, it aims to optimize drug prescription and evaluate drug safety through the choice of appropriate drug and dosage, based on biomarkers, and according to the particular conditions of each patient (consumption of other drugs, clinical and pathophysiological situation), in order to prevent adverse reactions and therapeutic

failures. Additionally, it provides a potentially useful tool in the personalized intelligent selection of individuals in clinical studies with drugs.

- **Medical Genome Pilot Project of Andalusia.**[11] Launched in 2010, this project has used genomic data to make more effective treatment decisions in conditions such as epilepsy and multiple sclerosis. The project addressed the sequencing of hundreds of human genomes from phenotyped sick individuals and control individuals, to develop the technologies that allow accelerating the process of discovering the genes responsible for a specific disease. The project focused on the study of rare diseases. Although they are isolated and uncommon conditions, as a whole they are important because they affect 5-7% of the population in developed countries.

- **Cantabria Cohort Project.**[17] Started in 2021 by the Marqués de Valdecilla Research Institute, it is a unique and pioneering study in Spain that will advance the understanding of diseases, thanks to the registration of health data and samples from volunteers. Its main objective is to provide knowledge about the main determinants of health and disease in the population of Cantabria, which will be key to the progress of precision medicine and the establishment of health strategies in the region.

- **Precision Oncology Program of Catalonia**.[54] Program published in 2021 by CatSalut and aimed at establishing a scope of action against all molecular or genetic alterations linked to prognostic markers, predictors of therapeutic response, the indication of a more effective drug for the patient, or the identification of alterations related to hereditary predisposition to cancer.

- **Galicia Precision Oncology Strategy**.[55] Published by the Galician Health Service in 2023, it is focused on advancing personalized precision medicine in the public healthcare system of Galicia and applying even more effective treatments for each type of cancer through the promotion of molecular diagnosis, targeted therapies to personalize treatments, and access to innovative therapies.

- **Galicia Genome Project**:[56] Announced in 2024, the project will collect the DNA of 400,000 people, with the goal of being able to detect diseases before they appear, diagnose them early, and offer individualized pharmacological treatments. These tests will generate essential information for the patient's medical history, but also valuable for research and understanding the genetic profile of the community.

- **Oncology Plan of Euskadi 2018-2023**.[57] Published in 2018 by the Department of Health of the Basque Country, it outlines the working lines to improve health outcomes in this disease, focusing its intervention strategies on 5 axes of action, with precision or personalized medicine being one of them. Among them is the establishment of a Committee for Planning and Management of Personalized Medicine in Euskadi for the evaluation of resources and functional decision-making and organization of healthcare with guarantees of quality and efficiency, as a tool for advising the Department of Health in the planning of Personalized Precision Medicine.

- **Personalized and Precision Medicine Plan Andalusia 2023-2027**.[58] Published in 2023 by the Ministry of Health and Consumption of the Andalusian Regional Government, it plans to establish a common portfolio of Personalized and Precision Medicine services that includes the necessary procedures, techniques, and healthcare benefits for its development and allows for the equitable improvement of disease prevention, diagnosis, treatment, and prognosis.

- **Integrated Personalized Medicine Strategy of Navarra**.[59] Published in 2021 by the Government of Navarra and aligned with the European Commission, its primary objective is to position Navarra as an international reference in Genomic Medicine applied to Personalized Precision Medicine through research excellence, providing significant socio-economic benefits to the people of Navarra, including a more efficient and sustainable healthcare system, economic growth, and the generation of quality employment.

- **Integrated Rare Diseases Plan of Castilla y León (PiERCyL) 2023-2027:**[60] Published in 2023 and included in the Personalized Precision Medicine Strategy of Castilla y León, it establishes a coordinated network system throughout the region and provides patients with equitable access to the most innovative resources, such as Whole Genome Sequencing from the University Hospital of Salamanca, a service already included in the Portfolio of Healthcare Services of the Community.

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