Perspective

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Personalized Medicine

The evolution of personalized healthcare and the pivotal role of European regions in its implementation

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Personalized medicine (PM) moves at the same pace of data and technology and calls for important changes in healthcare. New players are participating, providing impulse to PM. We review the conceptual foundations for PM and personalized healthcare and their evolution through scientific publications where a clear definition and the features of the different formulations are identifiable. We then examined PM policy documents of the International Consortium for Personalised Medicine and related initiatives to understand how PM stakeholders have been changing. Regional authorities and stakeholders have joined the race to deliver personalized care and are driving toward what could be termed as the next personalized healthcare. Their role as a key stakeholder in PM is expected to be pivotal.

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Since the 20th century medicine and healthcare have been radically transformed by technological progress, biomedical and clinical research achievements, and increased disease management capacity.

Over time, new paradigms of medicine and healthcare have been defined and an approach that genuinely tends toward the single person is technically feasible, economically valuable [1,2] and culturally, ethically and socially accepted: with time, it will more and more unethical and uneconomic to deliver nonpersonalized services considering the inefficacy, side effects and high costs of some standard treatment [3,4].

Principles of this personalization continuum have been traced from the scientific publications and complemented with an assessment of strategic documents released by European fora, which have a focus on personalized medicine (PM) such as the International Consortium for Personalised Medicine (ICPerMed). The concepts included in this manuscript and their relationships and connections are schematically represented in Figure 1.

Early approaches to PM

PM is not only about the mere individualization of medicine which, as a concept, was formulated by Hippocrates over 2400 years ago [5] but about the higher precision of diagnosis, therapy and prognosis that can ideally be tailored to the single patient and/or citizen [6].

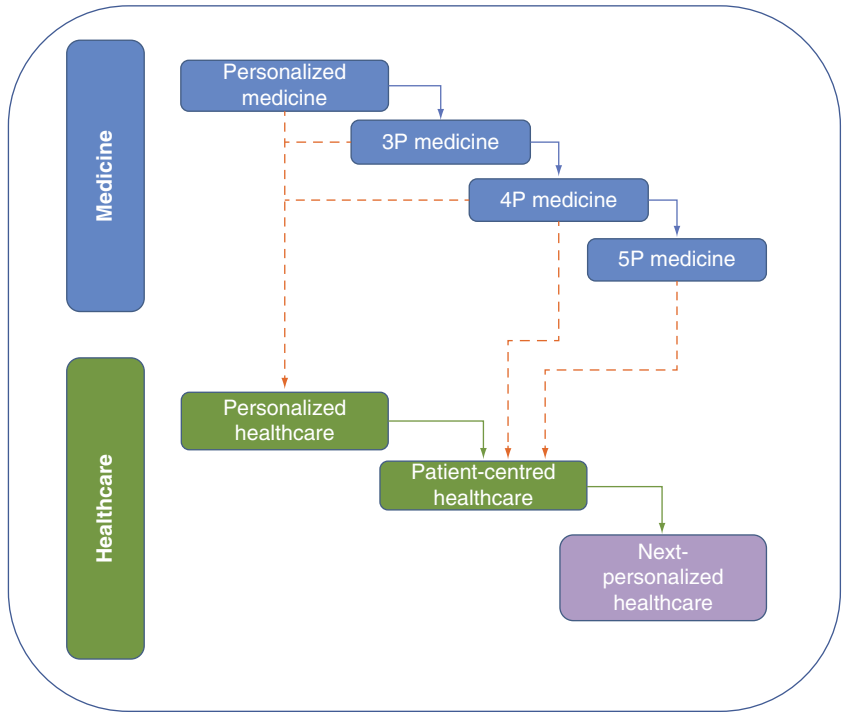

Figure 1. Evolution of personalized medicine and healthcare. Top (medicine): the horizontal movement depicts the evolution of personalized medicine approaches. Bottom (healthcare): the vertical evolution shows how the personalized medicine transforms healthcare, and how healthcare evolves (horizontal movement) toward the next personalized healthcare.

Throughout the course of history, western medicine frameworks have moved across three big families of approaches [7]:

- Disease-based approach (ancient): the patients were treated only when the disease was manifested; the diagnosis was mainly based on the signs and symptoms presented by the patients and treatment prescribed according to the experience, knowledge and intuition of the physician.
- Evidence-based approach (contemporary): diagnosis, therapy and care options for individual patients are guided and decided by the outcome clinical studies as well as medical guidelines, which have been developed based on biomedical and clinical research. With this approach, the combined knowledge of different areas of life sciences (clinics, biology, biotechnology and computational biology) contribute to the understanding of the mechanisms of diseases and the formulation and validation of the most appropriate therapy.
- Personalized approaches (person-specific): tailored to patients' characteristics such as genome, microbiome, epigenetic (precision) and lifestyle parameters, whose complexity can be captured into the so-called network medicine [8], evolving from the previous phase's computational biology) with emphasis on early and subtle signs of divergence from homeostasis and patients' sensitivity and awareness as well as personal preferences.

While practitioners have always deployed observable evidence to perform a diagnosis or deliver a treatment tailored to each individual, in the last decades technology provided new tools that are more precise and can probe not only the visually obvious but the very molecular makeup of each patient [9]. The deeper understanding of a patient's genetic variation can led the development and selection of drugs or care pathways that reduce potential side effects and therefore guarantee more successful outcomes [9]. High-throughput technologies have been driving the evolution of biology and medicine, allowing the identification of biomarkers using omics data alone or, more recently, in combination with environmental/lifestyle factors [10] lighting the vision of treatments tailored on the individuals: the era of PM began.

The evolving concept of PM

Although the knowledge behind it was already observable in clinical practice [11], the term PM first appeared in published works in 1999 [12], highlighting how the new technical advances in predicting health risks, tracking disease development and predicting response to therapy could enable tailored approaches to care. Over time, PM has served as a catch-all term that is often used synonymously with genomic medicine [13]. In 2009, PM was referred to by the President's Council of the White House Office of Science and Technology Policy (PCOST) – subcommittee on PM [14], as the "tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not" [9]. In 2014, the Horizon 2020 Advisory Group has defined PM as a medical model using characterization of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging and lifestyle data) to tailor the right therapeutic strategy to the right person at the right time, determine the predisposition to disease and deliver timely and targeted prevention. The definition has been adopted by the European Council Conclusion on PM for patients, which specified that "Personalised medicine relates to the broader concept of patient-centered care, which takes into account that, in general, healthcare systems need to better respond to patient needs" (2015/C 421/03). Upon the introduction of the Precision Medicine Initiative (PMI) by President Obama in 2015, these concepts have been used to identify which approaches are effective and for which patients based on genetic, environmental and lifestyle factors.

While the potential benefits of genomics and PM started to unfold, the concept of Predictive, Preventive and Personalized Medicine (PPPM or 3P Medicine) coined by Hood [15] was presented as the beginning of the new era in the medicine of the 21st century. Throughout the period 2003–2008, the term '3P Medicine' was used in the scientific literature predominantly in connection with genomics, pharmacology and systems biology, leading to the birth of scope initiatives to promote the concept and its implementation [16].

3P Medicine is also linked to the ability to demonstrate the value to the healthcare system, industry and patients. The 3P Medicine has inspired the scientific and clinical communities toward the vision of building a novel type of complex and interconnected healthcare, essential for the evidence-based care but also for the prediction of health risks, preventive even in apparently healthy individuals in order to avoid becoming 'a patient' [17]. The shift from the traditional, reactive approach that is focusing on disease treatment to preventative medicine aiming at maintaining health, including prediction of health trajectories and risk of disease development, is at this point a more tangible future.

3P Medicine has then morphed into the P4 Medicine concept, which includes participatory aspects [18], focusing on the important role that patients and patients' associations are playing in the evolution and implementation of PM, as active stakeholders in the health system.

The P4 vision of medicine is presented as a step in the direction toward a comprehensive concept that explicitly recognizes the role of the physical environment. Actionable examples of this approach are offered by the definition of the Flammer syndrome [19] and the potential for generalization of such an approach [20]. In this regard, the personalization process depends increasingly on multiple layers of data, which go well beyond genetics [21], echoing the words of Prainsack 'Genetics may still be the first violin in some contexts, but it is part of a bigger orchestra' [22].

To emphasize the psychological needs and values that make each individual unique [18], the idea of 5P Medicine has been formulated, with the 'fifth P' encompassing Psycho-cognitive aspects. In clinical practice, this implies going beyond disease-specific signs and symptoms typically collected by medical specialists, toward surveying early deviations from physiology at the general practitioners' level, leading to more subtle and early phenotyping. A fundamental exemplar is represented by the signs of low-grade inflammation and impaired wound healing [23,24], known precursors of all noncommunicable diseases currently among the major long-term threats to societal health.

PM in healthcare: a nonlinear progression from PM to next personalized healthcare

PM implementation requires a high involvement and commitment from the public sphere for its development and deployment – meaning the coordination of the wide range of policies and institutional players to govern and adapt the complexity of health systems to this new paradigm of treatment. This encouraged researchers and policy makers to analyze the potential embodiment of PM approaches within the healthcare, which refers, among others, to a reorganization of services, infrastructures, regulations and policies together with a plethora of stakeholders and investments able to bring PM in patients and citizen's hands. In this regard, the idea of a personalized healthcare

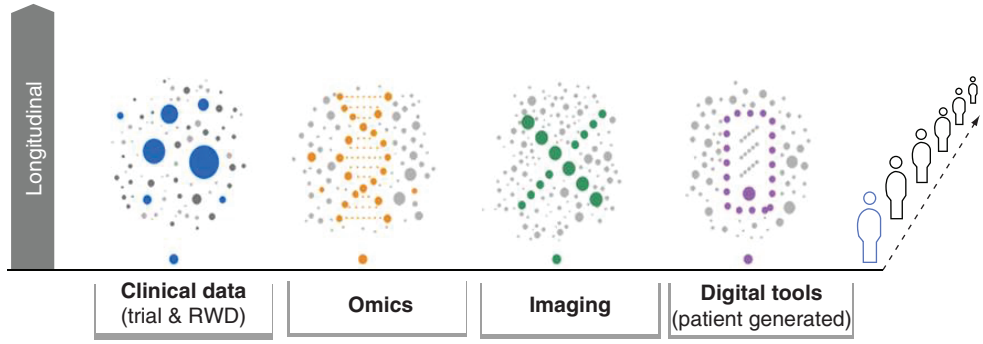

Figure 2. The building blocks of personalized healthcare.
RWD: Real-world data.
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(PHC) has come forward. The literature and definitions in this area are less mature. One of the first definitions identified within scientific publications mentioned PHC as the application of clinical know-how, concepts of systems medicine and PM technologies to improve health and minimize disease [25].

PHC is conceived as a coordinated and strategic medical model to patient care that applies systems biology as well as personalized, predictive, preventive and participatory care, and deploys technologies to tailor care across the health journey (Figure 2) [4,26].

PHC is characterized by a clear drive toward the use of health data for better clinical decisions and healthcare organization as well as by the strong commitment to resolve the ethical and practical challenges toward data exploitation for the translation of PHC into new healthcare solutions (the collection and standardization of heterogeneous datasets, the curation of the resulting clean data, citizens' consent for use of de-identified [anonymized and pseudoanonymized] data) [27].

PHC is presented as a solution for the long-term sustainability of healthcare, in an era where noncommunicable diseases account for up to 80% of healthcare costs [28], where pandemics such as COVID-19 have tremendous economic impacts and the European Stability and Growth Pact calls for acceptable budgetary performances [29].

PHC is considered the right approach to enable the potential efficiency gain locked in disease prevention, which, calculated as the median return of investment for public health interventions, is 14.3 to 1: each Euro invested generates €14.3 of return [30].

The focus of PHC moves from care to prevention and health-enabling progress in life expectancy, reducing health inequalities and funding of new treatments otherwise eclipsed by the increasing costs of avoidable illnesses [31]. Regarding the challenges PHC tackles, there is public trust: ensure that citizens are confident about sharing their data providing access not only to health records but also to health apps [32] and information services to support citizens' healthy choices; facilitate healthcare professionals' access to all the data (standardized, interoperable and processed into actionable knowledge) including the ones that have not been traditionally considered health information (apps and personal trackers); support healthcare professionals to make the best use of data and technology, enhancing decision-making processes.

In this context, regions in Europe have started considering PM as a strategic sector to drive innovation (Figure 3).

Person-centered care: the individual at the center of the healthcare system

The importance of the individual in terms of empowerment, clinical dialogue and shared decision-making has become more and more central in healthcare and the concept of person-centered care (PCC) has gained momentum in the scientific and policy debates. A general definition of PCC is not available, but common features associated with healthcare are traceable in the literature [34] such as a therapeutic relationship with the patient no longer based on a clinician-dominated dialogue [35], shared power and responsibility among health professionals and patients, person and citizen empowerment; trust and communication with the patients.

Patient outcomes such as Patient Reported Outcome Measures and Patient Reported Experience Measures have become an essential parameter to assess therapeutic strategies within PCC. At its core, PCC puts the complexity of the person and the great variability of people, acknowledging the individual dimension behind the patients, valuing

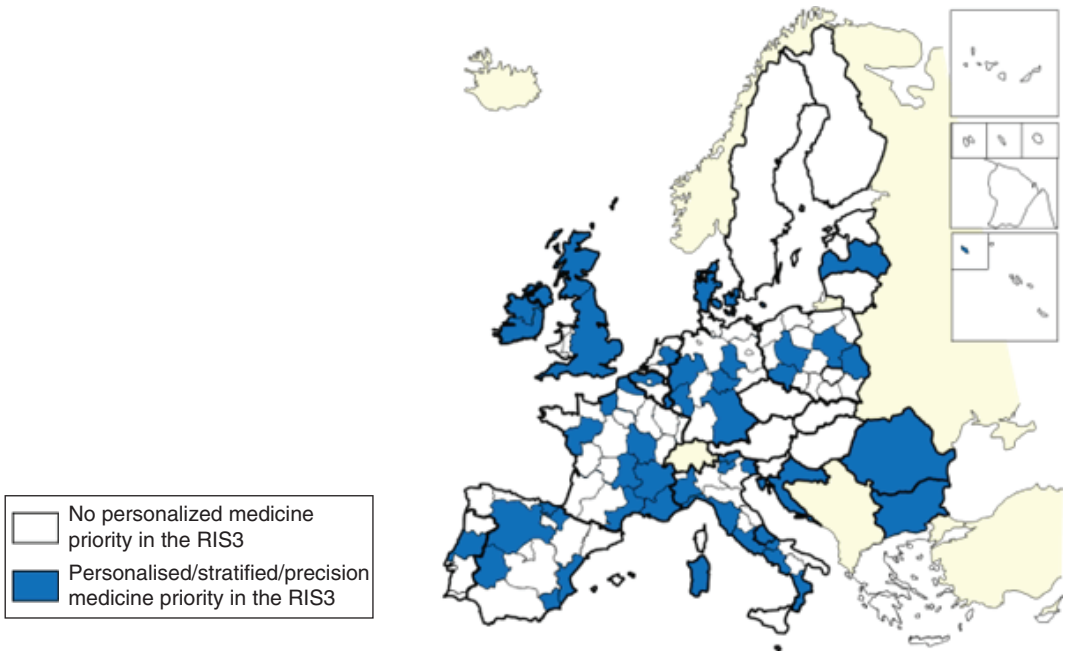

Figure 3. Eye@RIS3 visualizes public investment priorities for innovation across Europe. The figure depicts the regions that have included (in blue) personalized medicine as investment priority by European regions. Powered by Eye@RIS3 and shown by the European Commission within the Regions4PerMed international conference. Reproduced with permission from [33].

them and respecting their dignity and rights. Something that clearly unites PCC and PM is the ambition to move away from standardization and common guidelines toward strategies incorporating needs of the individuals [36].

The vision of a next PHC & its building blocks

The ability to measure, store and mine health-related data has reached unprecedented capacity, while public and private investments are flourishing in this area [37]. The abundance and affordability of genetic testing nowadays available, the plenty of e-health and m-health tools in clinical practice as well as wearable devices also offer the possibility to measure, collect and share [38] biological and lifestyle data easily. Smartphones and watches record social networks and capture behavior patterns [39]. All this, combined with electronic health records can provide an overview of health outcomes at various stages of life and convey health risks in individuals while improving health outcomes [37].

Universities, enterprises, policy makers and civil societies are relentlessly delivering new breakthroughs and new insights, which if coordinated and well valorized, could positively impact the health status of billions of people.

European strategic documents [40] and position papers of national and regional stakeholders [41] identify healthcare systems and healthcare authorities as the key players to push a further transition of healthcare as they set up and allow access to shared/centralized repositories to study inferences between different clusters of data, establish training programs for healthcare professionals, adopt wide healthcare reforms, empower patients in the comanagement and self-monitoring of their health, ensure financial sustainability.

A new configuration of healthcare system seems conceivable and, while it shapes itself, we have defined it as next PHC (nPHC): similarly to what occurred with medicine, we can expect an healthcare that includes personalized, predictive, preventive, participatory and person-centered care approaches. nPHC is concerned with the general population while focusing on the individuals' characteristics, an approach becoming increasingly necessary, especially considering world-wide healthcare emergencies, which have proven to hamper the social and economic stability globally: nPHC may have the potential in preventing epidemics from becoming pandemics through early applied measures, which would benefit from investments in smart and integrated care, central health data repositories as well as enabling technologies becoming a tool in support of public health.

The presence of robust, interconnected and accessible health data infrastructures such as biobanks, national and regional health registries, or clinical information repositories, will be a key feature of the nPHC: by collecting,

combining and effectively using data to deliver services to patients and citizen subgroups, nPHC can realize significant benefits for the society as a whole.

Multidisciplinary collaboration at international and inter-regional level through Partnerships (Public–Public and Public–Private) are additional key elements of nPHC. It might realize the full implementation of value-based pricing of novel therapies: resulting in reduced financial pressure on health systems, freeing the economic gains locked into prevention, predictability and participatory medicine, while delivering improved and more innovative services and leaving sufficient capacity for unexpected and unpredictable emergencies [42].

National and regional decision-makers acknowledge that the nPHC could be the right approach to tackle the main health and care challenges and have reinforced their activism in genomic initiatives, and health data infrastructures and healthcare reorganization [43].

The involvement of healthcare authorities is also fundamental to tackle the main ethical challenges underpinning the healthcare transformations such as data-sharing acceptance: as demonstrated by the contact-tracing apps to fight COVID-19 spread, in countries that made the use of apps voluntary, it seems that adoption has been low – and it is not due to restrictions that the General Data Protection Regulation (GDPR) imposes to data handling, considered that these apps typically do not collect or process data, as they do not rely on geolocation information, but instead use Bluetooth technology that notifies people if they have been in the proximity of someone who tested positive for the new coronavirus. It is actually the lack of citizen trust that is limiting the use of the apps and put endangering public health.

Besides that, for PM to be fully implemented and for the concept of nPHC to be realized, data-sharing aspects are indeed crucial. Patient data belong to patient and the access and use of those data outside of the clinical boundaries require patient consent [44]. These principles might slow down the exploitation of data held in clinical records and raise concern by regional and national data controller to let scientist access health-related data. While for retrospective research can be carried out on specific and anonymized data, once the study is finished the latter have to be destroyed. Form the big data standpoint, the idea of losing such amount of valuable data is a failure for the advancement of scientific and medical progress. Prospective consent of the patient to store and use data is a more effective model that can enable the storage of large datasets, then allowing the possibility to run research on this information [27]. In Europe, the GDPR, in force since 2018, applies when data controller (the entity that collects data), data processor (the entity that processes data) or data subject (the person) is based in the EU. This means that all studies performed by European entities and on European citizens are subject to the GDPR, with the exception of data that are fully anonymized. The GDPR has established seven basic principles to collect and use data: lawfulness, fairness and transparency; purpose limitation; data minimization; accuracy; storage limitation; integrity and confidentiality (security); and accountability. The GDPR establishes restrictions on data sharing, in other words, when a data controller intends to share data with another data controller, he/she needs to have an appropriate contract in place. Considering the fact that health data are sensitive, potential discrimination has the EU legislation has applied a balanced approach between privacy rights and the benefits of sharing for scientific purposes.

Within the GDPR, the data subject also has the right to oblivion (or right be forgotten): European citizen can withdraw the consent provided, after which the data controller needs to remove all personal data. While the implementation of GDPR has brought these aspects under the lens, it has not resolved the fundamental dilemma of protecting privacy or advance science. In this context, European Legislation is slowing the pace of progress connected to the data exploitation, compared with China and the USA [27].

In Europe, processing of data concerning health, genetic/genomic data and biometric data is not allowed unless one of following cases applies: data subject gives 'explicit consent', processing is necessary for the purposes of provision of services or management of health system, or processing is necessary for reasons of public interest in the area of public health [45]. This last point highlights the potential role of subnational (regional) authorities which can act as intermediate player between citizen rights, science and medical progress, providing balanced policy framework for data collection and sharing.

Vision for nPHC: how European regions are contributing to PM?

In order to reach higher performance, many member states (MSs) have started a process of governance healthcare decentralization in the last 30 years. This has distributed health power and responsibilities at subnational level improving, in many cases, the performance of the health systems around the main indicators [46] and the capacity of regions to drive health innovation.

Table 1. Overview of functions delegated to local and regional authorities by country. The table shows how in 24 out of 28 member states (UK still included), local and regional authorities enjoy a form of autonomy that can be leveraged to implement personalized medicine.

Member state	Legislative	Planning	Implementation	Funding	Member state	Legislative	Planning	Implementation	Funding
AT	✓	✓	✓	✓	IE	×	×	×	×
BE	×	✓	✓	✓	IT	✓	✓	✓	✓
BG	×	×	✓	✓	LT	×	✓	✓	✓
CY	×	×	×	×	LU	×	×	×	×
CZ	×	✓	✓	✓	LV	×	×	✓	✓
DE	×	✓	✓	✓	MT	×	×	×	×
DK	✓	✓	✓	✓	NL	×	✓	✓	✓
EE	×	×	✓	✓	PL	×	✓	✓	✓
EL	×	×	×	×	PT	×	×	✓	✓
ES	✓	✓	✓	✓	RO	×	×	✓	✓
FI	×	✓	✓	✓	SE	×	✓	✓	✓
FR	×	✓	✓	✓	SI	×	×	✓	✓
HR	×	✓	✓	✓	SK	×	×	✓	✓
HU	×	×	✓	✓	UK	✓	✓	✓	✓

✓ LRAs have a role × LRAs do not have a role.
LRA: Local and regional authority.
Image created with data taken from [47].

The current assets of health governance vary profoundly among MSs: according to the European Committee of Regions report [43], the health systems across Europe can be clustered in five types of European health management systems, which highlight the role of local and regional authorities (LRA) in the governance (see Table 1).

Subnational authorities all over Europe are essential players for effective (ability to improve people's health status) health and care systems [48]. They are directly responsible for the organization of public health, are involved in the territorial management of health systems and participating to healthcare spending (in 23 MSs out of the 28 mapped their contribution is higher than central governments) [47]. These characteristics make LRAs an important stakeholder to implement PM.

When it comes PM, in fact, LRAs in Europe are providing

- Funds for basic and translational research (also through joint funding schemes such as ERA PerMed project: where they cooperate with MSs and the European Commission (EC) bringing their regional key health priorities as core research topics; boosting career and retention of their scientists. Lombardy regions have recently kicked off a funding program completely dedicated to young researchers.
- Investments in regional personalized and genomic medicine initiatives (like the Navarra region NAGEN 1000 initiative: an example of a Project for Regional Implementation of Personalised Genomic Medicine in Healthcare [43]).
- Investments in health data platforms to collect in a standardized and homogeneous manner population health data to perform epidemiological analyses and plan public health interventions, like Tuscany region where the central TIX (Tuscany Internet eXchange) Data Center collects and processes health data from all healthcare providers on the territory.
- Implementation of regional strategies with PM at its core [49].
- Reorganization of healthcare systems according to the population epidemiology and health needs and setting up appropriate training for healthcare professionals [50,51].

Access to health information, such as the data as a service implemented by Lombardy region where accredited researchers can perform data-driven analyses on the regional data information hub. The data as a service created a secured virtual desktop environment where researchers can perform data analyses by their working environment [43].

The importance of LRAs in PM and in the nPHC appears to be directly connected to the level of autonomy they enjoy in key areas since they are, at different levels, able to define, lead and implement policies in healthcare delivery, as well as being in charge of health financing and resource organization, while able to respond to health priorities reflecting individual LRA characteristics and goals.

LRAs in nPHC are driving investments in technological infrastructures (biobanks, heath data repositories, data integration and interoperability) all over Europe [43].

Regions are also very active in including PM and this new configuration of PHC within their smart specialization strategies, which is a pillar of the European Cohesion policy of the EC, adopted to identify the most critical and promising areas for investments based both on the understanding of potential of the economy and on the so-called Entrepreneurial Discovery Process with wide stakeholder involvement. This reinforces the idea that regions are designed as a driver well-being and economic growth through PM.

All these considered, the idea of a modern healthcare needs LRAs at its core. LRAs provide value in the implementation of the nPHC, driving scientific research (which entails interdisciplinary, generation of new knowledge and management of disruptive innovation); translational research, genomic and PM initiatives; reorganization in the current health systems; regulatory aspects; health policy settings, in terms of principles, new needs and new knowledge to implement them; adaptation of general policies to different epidemiological as well as cultural management and socioeconomic conditions.

Therefore, in order to not disperse the great effort that European LRAs are producing in nPHC approaches, and multiply the benefits for the society, it is key that more coordination activities are organized among the regions and between subnational and central governments.

The strategic importance of LRA is also acknowledged by the Coordination and Support Activity called PerMed funded by EC until 2015, which supported and stimulated policy makers, researchers and health systems in Europe to develop further the concept of PM. Thus, European MSs, Third Countries and more recently European regions have contributed to and implemented the Strategic Research and Innovation Agenda (2015). Furthermore, the EC organized an important conference, together with all engaged MSs in June 2016. This laid the first stone of stronger pan-European collaboration between national and regional authorities and inspired the establishment of ICPerMed.

ICPerMed has with time evolved and issued strategic documents to foster PM (action plan and vision paper). With support of the EC and the participating MSs, a big 'Family' of PM-inspired initiatives has been established over the last 3 years. For example, the ERA-Net Personalised Medicine (ERA-PerMed), a consortium on Healthcare- and pharma-economic models adapted to personalized medicine (HEcoPerMed) as well as plenty of research and innovation projects and consortia. Furthermore, two regional consortia are funded by the EC: Regions4PerMed and SAPHIRE as well as a Europe with Latin American and Caribbean countries project (LAC, EULAC PerMed) and recently to consortia to foster the collaboration on PM between the EU and China: SINU-EU PerMed and IC2PerMed (see Figure 4).

Conclusion

The context presented herein highlights how the early concepts of PM are morphing in what we have now termed nPHC, intended as, but not limited to, Personalized, Predictive, Preventive, Participatory and Person-centered approaches that enable system transformation through the direct involvement of citizen, patients, policy maker, academia and industry for an effective and sustainable planning, implementation and delivery of PM services.

Regional authorities and stakeholders have joined the race to deliver personalized care, bringing value in terms of investments, infrastructures, educational and policy frameworks complementing efforts carried out at national level.

LRAs are of fundamental relevance in the potential development of the nPHC, due to their characteristics and their organizational models in Europe.

European regions in all MSs play a pivotal role in the nPHC and have become in the last decade key stakeholders in the field and more and more central in the public debates.

LRAs are a driving force of Health Research, Innovation and Healthcare modernization and need to be engaged in joint and coordinated policies in Europe to avoid fragmentation, ensure successful development of strategic initiatives and multiply benefits for citizen, industry academia and policy makers.

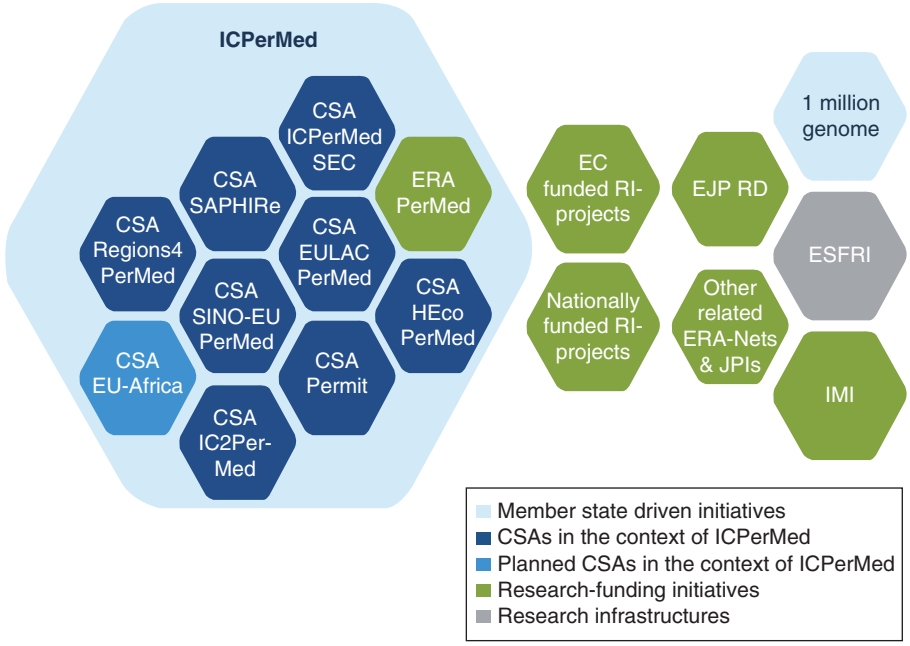

Figure 4. The recent International Consortium for Personalised Medicine 'Family'.
CSA: Coordination and Support Action; EC: European Commission; EJP RD: European Joint Programme on Rare Diseases; ESFRI: European Strategy Forum on Research Infrastructures; ERA: European Research Area; EULAC: European Latin America and Caribbean Foundation; IMI: Innovative Medicine Europe.
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Future perspective

nPHC is a concept that allows science, industry, citizen and policy makers to effectively work together to bring the benefits of PM in citizens' hands, reducing barriers to development of science and technology, providing adequate levels of investment a balanced policy framework to keep healthcare systems sustainable while delivering high-quality PM services. nPHC is the concept that allows clinician, scientists, technology provider and citizen to free the untapped medical and economic value in personalized care.

Within the next framework program for research and innovation 2021–2027, called 'Horizon Europe' the EC plans to set up European Partnerships with MSs, including the private sector, foundations and other stakeholders. The goal of these pan-European consortia will be to deliver on global challenges and industrial modernization through concerted research and innovation efforts. One of these partnerships could be built on PM, with the aim to accelerate the uptake of research and innovation results into clinical practice and prevention strategies. Thus, to secure Europe's position in state-of-the-art healthcare provision, facilitate a shift from a 'one size fits all' approach toward taking into account individual differences and better utilizing the accumulating data to manage health, disease and its predisposition, promote sustainable health systems and independence in data intensive healthcare.

ICPerMed family as well as other initiatives will support the development and implementation process of such a partnership. This will be a European approach with impact not only across the disciplines but also cross-sectional. Therefore, European regions will and should have a crucial and active part in this partnership, especially when it comes to implement PM approaches into the health systems and therefore the nPHC, coinvestments in transnational research, technology transfer and market access of new PM and healthcare approaches, products and services.

LRAs, considered the capability to implement important pilot initiatives, should be a cornerstone of important infrastructural strategies at EU level such as the European Partnership on Personalised medicine, the European '1+ Million Genomes' Initiative as well as the Health Research and Innovation Cloud.

In order for these initiatives to be successful, it will be essential to include the vision of nPHC and involve and leverage the regional dimension.

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Executive summary

The evolution of the concept of personalized medicine

- In the last decades, the evolution of medical practice has moved from a traditional, predominantly reactive and disease-based approach, toward a P (Personalized, Preventive, Participatory, Predictive and Population-based) medicine. This was possible thanks to the achievements in all areas of personalized medicine (PM) enabled by the rise of genomics, data generation and valorization as well as improved disease management and computational capacities. New tools for clinical decision flourished making medicine able to prevent and anticipate diseases' onset, identify health risks, predict response to therapy, thus reshaping care models and fundamentally improving healthcare capacity.
- As PM becomes a strategic goal for national and regional policy makers, its implementation encompasses a wider plethora of stakeholders than traditional scientists, such as technology providers, regulatory, healthcare and public health authorities, companies. All over Europe, there is a push to reorganize the PM value chain at central and local levels in order to reduce fragmentation, increase investments in shared infrastructures, ease collaboration between science and industry and thus accelerate the pace to deliver personalized care.
- As great policy functions are delegated at regional and subnational levels all over Europe, new institutional stakeholders join the debates on PM harbingers of prodromal yet radical changes in medicine and healthcare.

Methodology

- In order to capture the milestones of the evolution of PM and outline the boundaries of a future personalized healthcare (PHC), in the first part of this manuscript, we perform a review of the conceptual foundations for PM through scientific publications: As there are over 42,000 papers on the topic (using 'precision medicine' and 'Personalized Medicine' as MeSH terms in PubMed database), we focused on documents where a clear definition of PM and PHC is identifiable. We have summarized this continuum in:
  - Early approaches to PM.
  - 3–5P Medicine.
- Then, we sketch how the impact of the evolution of PM on healthcare organization has been impacted by PM approaches over time identifying the basic features of:
  - PHC.
  - Patient-centered care.

The formulation of a new concept of PM

- Furthermore, we try to outline the building blocks of a novel concept of PHC, where new institutional stakeholders are playing a leading role and within which policy makers will be prompted to design and implement feasible PM approaches in the existing and very diverse health systems.

The involvement of regional stakeholders

- Lastly, we describe how European Local and Regional Authorities are being active in PM and are expected to act as the key enabler of these transformations and recommend a greater integration of the latter within the current and future strategic initiatives in Europe.

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