



# Predictive, Personalized, Preventive and Participatory (4P) Medicine Applied to Telemedicine and eHealth in the Literature

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## Abstract

The main objective of this work is to provide a review of existing research work into predictive, personalized, preventive and participatory medicine in telemedicine and ehealth. The academic databases used for searches are IEEE Xplore, PubMed, Science Direct, Web of Science and ResearchGate, taking into account publication dates from 2010 up to the present day. These databases cover the greatest amount of information on scientific texts in multidisciplinary fields, from engineering to medicine. Various search criteria were established, such as (“Predictive” OR “Personalized” OR “Preventive” OR “Participatory”) AND “Medicine” AND (“eHealth” OR “Telemedicine”) selecting the articles of most interest. A total of 184 publications about predictive, personalized, preventive and participatory (4P) medicine in telemedicine and ehealth were found, of which 48 were identified as relevant. Many of the publications found show how the P4 medicine is being developed in the world and the benefits it provides for patients with different illnesses. After the revision that was undertaken, it can be said that P4 medicine is a vital factor for the improvement of medical services. It is hoped that one of the main contributions of this study is to provide an insight into how P4 medicine in telemedicine and ehealth is being applied, as well as proposing outlines for the future that contribute to the improvement of prevention and prediction of illnesses.

**Keywords** eHealth · Predictive · Personalized · Preventive · Participatory · Telemedicine

## Introduction

P4 medicine describes a focus on systems that include predictive, personalized, preventive and participative aspects [1]. It proposes the integration of numerous points of biological data, which include longitudinal molecular, cellular and phenotypical

measurements, as well as individual genome sequences, in order to better define the health or wellbeing of every person, predict transitions to illness and orient medical interventions [2, 3]. The implementation of P4 medicine from a clinical point of view will create predictive and personalized models that represent the wellbeing of every patient or of a disease, which enables the design of new pharmacological tests that take into account the heterogeneity of responses to therapies and the stratification of the illness [4, 5].

Computer technology has been applied to various domains in order to obtain a greater yield. From the point of view of preventive medicine, portable devices are useful for monitoring and warning. Building a software system that facilitates monitoring and warning is one promising solution for promoting preventive medicine [6, 7].

The future of health services is centered on offering people a complete image of the many factors that affect their health. Real-time analysis enables doctors, researchers and other interested parties to take the most informed decisions, at the same time as offering patients greater control over their own medical attention [8, 9]. Cognitive computing constitutes a new evolution of algorithms and systems with language-

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neutral programming (LNP), the creation and evaluation of hypotheses and dynamic learning. The advances in the availability of data, connectivity and cognitive computation are enabling doctors, researchers and other health professionals to personalize their service with greater diagnostic certainty [10].

P4 medicine currently promises to provide a revolutionary new biomedical focus that is holistic instead of reductionist [11, 12]. With the rapid development of high-performance technology, an explosive accumulation of biological information is gathered on multiple levels of biological processes, which include genome, transcriptomic, proteomic, metabonomic and interactomic information (-omics). The implementation of an integrative analysis of these multiple -omics data is the best way of obtaining systematic and complete views of all living organisms, achieve a better understanding of the mechanisms of the illness and find personalized and applicable health treatments [13].

In this study, we present an overview of the state of the arte regarding predictive, personalized, preventive and participatory medicine in telemedicine and ehealth, with the aim of obtaining a better general view of the area and of proposing new lines of research with applications of personalized medicine in health.

There are similar studies in existing literature that show the viability of our study, such as: [14] in reference to the appearance of P4 medicine, implications for society, including the ability to revert to the growing costs of medical attention; [15] presenting an overview in which the fundamental conceptual bases are established and the main aspects of P4 medicine are discussed; and in [16], in which an overview of the potential of P4 medicine for predicting and preventing illnesses is presented, in a revolution which will be personalized in its nature, essentially probabilistic and participative.

The points that will be covered in this paper are as follows: firstly, the methodology that has been followed to identify the papers related with predictive, personalized, preventive and participatory medicine in telemedicine and ehealth; secondly, the results obtained from the review and finally, the discussion and conclusions drawn from the work will be developed.

## Methodology

### Databases

In this study, a review was made of the existing research work into predictive, personalized, preventive and participatory medicine in Telemedicine and eHealth published between 2010 and the current day. The databases used for searches are the following: Science Direct, IEEE Xplore, Web of Science, PubMed and ResearchGate, taking into account publication dates from 2010 up to the present day. These

databases cover the greatest amount of information on scientific texts in multidisciplinary fields, from engineering to medicine, and they facilitate finding articles in scientific and academic magazines, or in repositories, archives and other collections of scientific texts.

### Inclusion criteria

As inclusion criteria for the search on said databases, the following key terms were used: “Predictive” OR “Personalized” OR “Preventive” OR “Participatory” AND “Medicine” AND (“eHealth” OR “Telemedicine”) in both Spanish and English. The said terms were searched for mainly in Title/Abstract, published from the year 2010 to the present day. In Table 1 the search strategy used in this investigation is shown, and the criteria used are provided specifically by the search engine itself for the databases.

### Studies selection

In order to carry out this review, the Prisma [17] methodology was used. The selection of the articles was carried out by reading the titles and the summaries of the results obtained, and those papers were classified by reading their summaries and the whole article where necessary. In order to classify the articles, the following criteria were considered: 1) general P4 medicine studies applied to telemedicine and ehealth; 2) studies about predictive, preventive, personalized and participatory medicine in telemedicine and ehealth, both individually and intertwined; 3) discarding those studies that focus on how P4 medicine is undertaken in certain countries. All the repeated articles in more than one database will be discarded. The diagram used in the review is shown in Fig. 1.

Of the 184 publications found, 45 were duplicates or with titles irrelevant to this investigation. The remaining 139 studies were read and their summaries analyzed to determine which were of interest, obtaining a final result of 48 documents that provided pertinent contributions. In the following section the most relevant papers found are shown.

## Results

With an increasingly older population, the prevalence of chronic illnesses and the increase in costs have created some unique health challenges for our global society. In response to these unmet health care needs, researchers are actively seeking innovative solutions that center on [1] prevention of illness and, [2] personalized diagnosis and treatment. It is predicted that taking preventive measures for the control of health and diagnosing and treating patients with a personalized focus in the early stages of the illness will make care more viable and sustainable [18].

**Table 1** Search criteria in different databases

Keywords/Database	Science direct	Web of Science	PubMed	IEEE Xplore	ResearchGate
Predictive Medicine AND eHealth OR Telemedicine	“title”	“title”	“title/abstract”	“title”	“title”
Personalized Medicine AND eHealth OR Telemedicine	“title”	“title”	“title”	“title”	“title”
Preventive Medicine AND eHealth OR Telemedicine	“title”	“title”	“title”	“abstract”	“title”
Participatory Medicine AND eHealth OR Telemedicine	“title”	“title”	“title”	“abstract”	“title”
Predictive AND Personalized AND Preventive AND Participatory Medicine AND eHealth OR Telemedicine	“title/abstract”	“title”	“title/abstract”	“title/abstract”	“title”
P4 Medicine AND eHealth OR Telemedicine	“title/abstract”	“title”	“title”	“title/abstract”	“title”

The development and application of P4 medicine for biology and illnesses are transforming medical research and clinical practice at an unprecedented rhythm. The convergence of these practices will enable the precise prediction of susceptibility to the illness and early diagnosis for a processable preventive outline, as well as personalized treatment adapted to each individual [19]. From a total of 48 relevant papers in our review, we found 14 papers about P4 medicine in general terms in telemedicine and ehealth (See Table 2).

The challenges for today’s bioinformatic scenarios are the heterogeneous collection of users in different places, the distribution of large and heterogeneous data sources, multi-computer environments and the complex chains of processes for analysis [23].

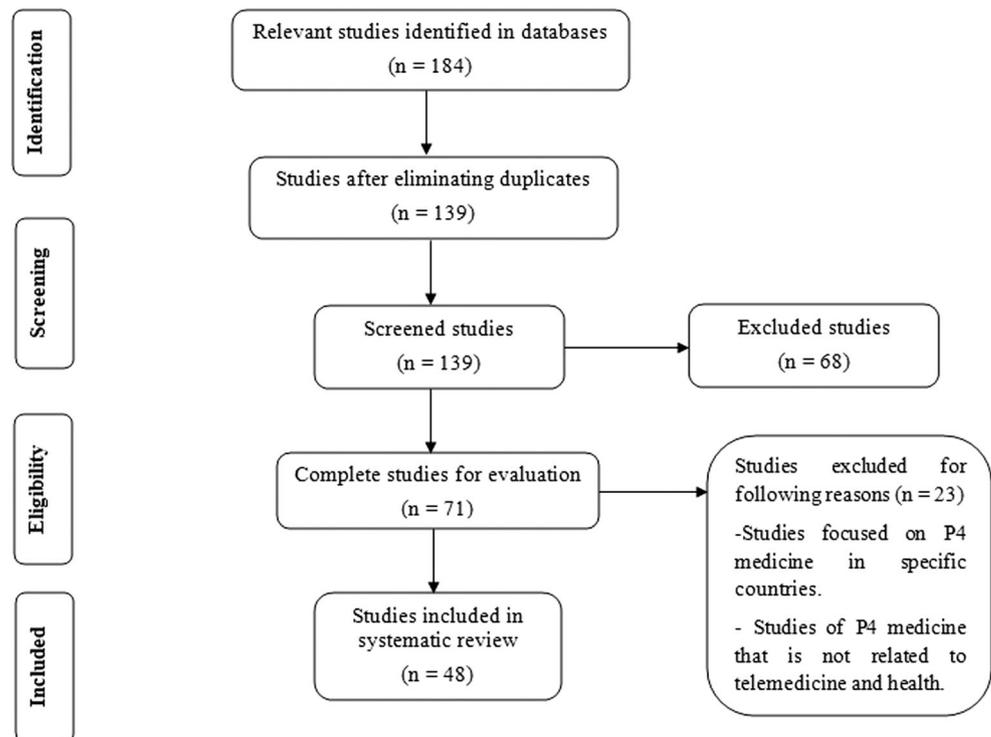
Medical genetics and the studies of genetic variation are related to health and human illnesses: consciousness and abilities in DNA and genome sequencing make it possible to

study the molecular sequences associated with many human illnesses, to predict, personalize, prevent and/or treat various afflictions [31].

**Predictive medicine**

Predictive diagnoses for the early treatment of complex illnesses such as Alzheimer’s, cancer, cerebrovascular accidents, diabetes mellitus or chronic renal and cardiac illnesses constitute clinical heterogeneity. The methods of conventional diagnosis based on measuring just one parameter encounter the danger of low sensibility for differentiating with precision those patients with highly heterogeneous clinical manifestations [32]. Although predictive diagnoses are conventionally represented by methods and tests based on the genome, image markers form an integral part of the medical diagnosis, particularly for the diagnosis of neurological disorders.

**Fig. 1** Flow diagram



**Table 2** Studies of the bibliographic review related to P4 medicine in telemedicine and ehealth

Authors	Year of publication	Study proposal	Results
Bengoechea [20]	2012	They establish the conceptual bases and analyze the main aspects of P4 medicine within the frame of infectious diseases.	<ul style="list-style-type: none"> <li>- P4 medicine is fed by system focuses for illnesses, which include methods for personalized sequencing of the genome and new computational techniques for building dynamic predictive networks of illnesses from massive quantities of data.</li> <li>- Its use in infectious diseases will provide multiple benefits for both patients and the healthcare system.</li> </ul>
Persch, Braveman, & Metzler [21]	2013	They show how P4 medicine offers a model for pediatric occupational therapy professionals. Expert use of research and the data of occupational therapy professionals contribute to predictive medicine.	<ul style="list-style-type: none"> <li>- The practice of occupational therapy centered on the patient is in line with the concept of personalized medicine within the P4 model and helps to promote the health of children and prevent disability.</li> </ul>
Poon et al. [18]	2013	They present cutting-edge technologies in the emerging field of health information for preventive medicine and personalized healthcare.	<ul style="list-style-type: none"> <li>- The contributions include advances in systems of sensors and acquisition, management systems of personal and hospital information and a future platform for administrating healthcare in a ubiquitous and discreet way, as well as intelligent systems for backing up the use of information in health.</li> </ul>
Shapira [22]	2013	They present a study of nutrition of gender within predictive, preventive and personalized medicine. With the aim of obtaining differential metabolic responses, particularly in women. Illnesses such as diabetes, cardiovascular diseases and certain cancers suggest the need for different metabolic and chronological perspectives for their prevention and intervention.	<ul style="list-style-type: none"> <li>- The results show that the differential metabolic responses of women have caused a gender effect in biochemical-endocrinological patrons, the metabolic mechanisms and the risk factors, emphasizing the importance of more specific prevention strategies for each gender.</li> </ul>
Wegener et al. [23]	2013	They present a focus towards developing an environment of data mining for personalized medicine.	<ul style="list-style-type: none"> <li>- The focus points at tackling the needs and requirements for applying data mining techniques to bio-information solutions in the context of P4 medicine.</li> </ul>
Miralles et al. [24]	2014	They evaluate the potential of P4 medicine through the Synergy-COPD project to create awareness surrounding the underlying mechanisms of chronic obstructive pulmonary disease (COPD).	<ul style="list-style-type: none"> <li>- The results showed the high potential of P4 medicine focus for tackling the heterogeneity observed in patients both in terms of clinical manifestations and progression of the illness.</li> </ul>
Bresó et al. [25]	2015	They present a web patient empowering system (PHSP4) which guarantees the continual monitoring and evaluation of the state of health of patients with Diabetes Mellitus (DM) (types I and II). PHSP4 is a Personal Health System Based on Knowledge (PHS) which follows the tendency of P4 medicine.	<ul style="list-style-type: none"> <li>- The results show the trustworthiness of the system and the high acceptance rate by healthcare professionals.</li> <li>- It provides messages to outpatients and doctors about the achievement of objectives, the following of adjusted treatments and the condition of the patient.</li> <li>- It calculates a vector of risk of four components of the pathologies associated with DM: nephropathy, diabetic retinopathy, diabetic foot and cardiovascular event.</li> </ul>
Guzzi et al. [26]	2016	They present a review of computational tools and focuses to analyze selected -omic data, with a special focus on microarray data and mass spectrometry, which can be used to back up P4 medicine. They describe some applications of preventive medicine (discovery of biomarkers) and personalized medicine (pharmacogenomics).	<ul style="list-style-type: none"> <li>- The results show that -omics sciences, and, in particular, the whole line of analysis of -omics data, is becoming a cornerstone of P4 medicine, and currently there are many positive examples of P4 medicine presented in said review.</li> </ul>
Kodrič et al. [27]	2016	They present a systematic review of four different types of “-omics” studies related to osteoporosis, with the aim of discovering new predictive, preventive, diagnostic and curative objectives for better management of the geriatric population.	<ul style="list-style-type: none"> <li>- They identified five genes (ESR1, IBSP, CTNBN1, SOX4 and IDUA) and processes such as the Wnt route, JAK / STAT and ERK / MAPK markers, which need further validation of their predictive, diagnostic or other clinical value in osteoporosis.</li> <li>- This molecular information will enable the adaptation of osteoporosis to P4 medicine strategy and could increase the effectiveness of the prediction and prevention of illnesses, while decreasing the sickness rate among geriatrics.</li> </ul>
Vogt, Hofmann, & Getz [28]	2016	They prove that through patent which describes a method of systems medicine, P4 Medicine will be able to	<ul style="list-style-type: none"> <li>- The results show that P4 medicine is promoted like an advert from an era of transformational scientific</li> </ul>

**Table 2** (continued)

Authors	Year of publication	Study proposal	Results
Mota [29]	2017	develop a scientific and quantitative metric for the wellbeing of patients which removes supposed vagueness, ambiguity and incompleteness in health. They prove through prevention studies that diabetes can be prevented in a limited population.	objectivity, its definition of health is still based on the guidelines, and as such it is open to the influences of scientific, philosophical and political questions. - The results show that P4 medicine can provide incalculable benefits both for the general population and for the limitation of the enormous costs associated with treatment and prevention. Prevention programs are more recommended than ever to be used across the population, regardless of risk.
Sagner et al. [30]	2017	They propose a “P4 Health Continuum” model as a framework for promoting and facilitating the collaboration of multiple interested parties with an orchestrated common language and an integrated healthcare model for increasing health; taking P4 medicine into account.	- The results show that this P4 medicine focus requires an orchestrated language to help researchers, healthcare professionals and interested parties in a multitude of sectors to collaborate in the most efficient way possible, thereby guaranteeing wellbeing and prolonging the life of the patients.

In Table 3, the results obtained in reference to predictive medicine in telemedicine and ehealth is shown.

### Preventive medicine

The main objective of the preventive measures against complex illnesses is to identify the people at risk well before the development of the symptoms of the illness, so that preventive treatments can be planned. In consequence, the preventive biomarkers have as their objective to detect a population and stratify the individuals with a high risk of developing an illness by measuring the association between their molecular profile and the illness phenotype [32]. In Table 4, the results found in literature referring to preventive medicine in telemedicine and ehealth is shown.

### Personalized medicine

Personalized medicine is a field of healthcare in rapid growth. Its advantage is the availability of clinical, genetic, genome and environmental information unique to each person [43, 44]. The medical attendance that incorporates personalized medicine provides a coordinated, continuous service based on the data of the patient [45]. The objective of personalized medicine is to promote the wellbeing of health, satisfaction, sensation of security and to increase the possibility of a successful prevention, detection and treatment of an illness [46, 47]. This form of medicine, as well as the patient’s personal data and biological measurements of medicine, uses genome information data to understand the molecular structure of the illness and optimize the healthcare strategies and pharmacological treatment [48, 49]. In areas like oncology, the link between the clinical data and the genome information could result in the

development of clinical-molecular profiles that improve further still personalized oncological healthcare [50, 51].

In Table 5 the results obtained for personalized medicine in telemedicine and ehealth are shown.

### Participatory medicine

In parallel to the concepts of personalized medicine and directed treatment, medicine centered on the patient is being developed based on patient-oriented research [59]. The objective of patient-oriented research is to identify the best treatment strategy guided by the diagnostics of heterogeneity of the illness [60]. The internet has facilitated the participation of individual patients in healthcare when sharing their experiences in blogs and other social media, which is why communities of patients online represent a real model for participative medicine [32].

Within health disorders, asthma is a good candidate for participative medicine focuses since current medical guides provide self-control of the illness on the part of patients who are informed and enabled for TIC. In [61], they center their work on applications for m-health for patients with asthma and on decentralized monitoring of air quality by the patients themselves using accessible and available hardware platforms based on Arduino. The results show the creation of a light and accessible air quality sensor that uses an architecture based on the cloud for adding and analysing the readings.

### Discussion and conclusion

In recent decades, computational methods have helped enormously in the analysis of biological information. The new post-genome era, computational analysis will play a vital role

**Table 3** Studies related to predictive medicine in telemedicine and ehealth

Authors	Year of publication	Study proposal	Results
Simon [33]	2010	They present designs for clinical trials for the development of new treatments with predictive biomarkers. They describe a focus based on prediction for the analysis of random clinical trials that seems to be greatly superior to post hoc subset analysis.	- This focus is of great potential value for controlling the costs of society on healthcare. The development of treatments with predictive biomarkers requires significant changes in the standard paradigms for design and clinical trial analysis.
Wang & Wong [34]	2013	They present a focus called ACP which combines methods which are artificial (societies), computational (experiments) and parallel (execution) for intelligent systems and technology for predictive medicine.	- The results show that the methods based on ACP provide a low-cost platform that is trustworthy and flexible for the control and administration of the medical systems from a system perspective. - The development of this framework in integrated medicine, fed by close collaboration between doctors, engineers and scientists, will bear fruit in the form of preventive and predictive practices of a personal, proactive and precise nature, which include rational combinatorial treatments, adaptive care and patient-oriented illness management.
Pham et al. [35]	2017	They present DeepCare, a dynamic neuronal network that is deep from one extreme to the other, reads medical registers, stores previous history of illnesses, infers current states of illness and predicts future medical results. In order to achieve predictive precision and power, DeepCare extends classic memory to long-term memory, incorporation discreet admissions of variable size in the vectorial space, parametrizing the time to enable irregular time, incorporating interventions to reflect its specific influence on the course and progression of the illness.	- The results show that DeepCare is capable in the prediction of the following phases of the illness, recommending interventions and determining unplanned readmission among patients of diabetes and mental illnesses.
Tuck et al. [36]	2017	They show how the time-dependent risk factors, interaction and repetition can be used to create a more precise predictive medicine. Example: they show how the appearance of anemia can be predicted from the clinical history of electronic health registers.	- Using the codes of Version 9 of the International Clinical Diagnoses organized into 25 main diagnostic categories, they measure the progression of the illness, examining the changes to the risk long term, the interactions in the risk of combinations of illnesses and the elevated risk associated with repeated hospitalization for the same diagnostic category.

in the integration of multiple -omics data to achieve personalized medical technology [13].

With the development of our study, we obtained a total of 48 relevant results that show us the level that P4 medicine in telemedicine and ehealth has reached. P4 medicine represents an explosive new form of tackling different illnesses in health such as: Alzheimer's, cancer, myopenia, cardiovascular illnesses, diabetes, etc. It's clear that the antiquated focus of medicine that was based on the illness will change during the next decade to personalized medicine in which the genetic composition of the person, and other molecular characteristics, will determine the focus for the treatment of the illness [62]. Modern medicine lacks precision in diagnostics and treatment: personalized medicine will alter modern medicine, putting emphasis on the patients, their genes, their environment, their response to treatments and their participation in their own care.

The ubiquitous convergence of mobile applications, the new smart sensors and automatic learning methods make it

possible to create automatic detection systems and pathology detection in the healthcare of a new generation [63]. These systems will help to create more effective and adaptive treatment platforms to the person, which they consider the "medicine of the future".

Clinical research that generates hypothesis has the potential to provide data that will illuminate the whole spectrum of genotype-phenotype, removing the bias that has limited this understanding in the past [64]. The application of these principles to clinical medicine may provide new routes for diagnosis and provide the theoretical base for predictive medicine that can detect the susceptibility of the illness and enable health to be maintained, instead of centering only on the treatment of the evident illness.

The developments in the area of pharmacogenetics / pharmacogenomics can help doctors achieve the target of personalized medicine, since personalized medicine will come to mean not only the right medication for the right person, but the

**Table 4** Studies related to preventive medicine in telemedicine and ehealth

Authors	Year of publication	Study proposal	Results
Swan [37]	2012	They present a vision and a plan for the undertaking of preventive medicine by 2050. They examine the efforts already underway, such as participative health initiatives, the era of big data in Health and the qualitative changes in mentality of society.	- The results show that preventive personalized medicine could be fundamental in resolving a great number of problems in the health sector.
Filipova-Neumann & Hoy [38]	2014	They develop a method for analyzing the implications for wellbeing of a genetic test that generates improved information about the type of specific risk of the person (for example: the predisposition of the illness to appear).	- The result of the genetic test can affect the intensity of the vigilance of the individual, as life goes on, in detecting any possible recurrence of the illness at an early stage. - The continuing costs of live depend as much on the genetic type of the person as on the option of treatment where the treatment behaves as a preventive measure against recurrence.
Finch et al. [39]	2015	They present a study on the use of text messages in the prevention of skin cancer	- The results show through the study how text messages about skin cancer prevention and early detection are new and acceptable to induce a behavior change in young Adults.
Nohara et al. [40]	2015	They present a study of a preventive medical service combining controls for eHealth and teleconsultations. They evaluate the rules of stratification and the short-term effects of the intervention.	- The results show that the eHealth system, which combines a health check and a teleconsultation over the mobile network, is an efficient tool in the system of social healthcare.
Hengartner et al. [41]	2016	They study the relevance of personality, with the objective of evaluating easily and viably whole populations to search for a greater risk of probable conduct of health deterioration, deficient environmental resources and, in particular, propensity towards mental disorders. They present a study of a preventive medical service combining eHealth controls and teleconsultations.	- These data help to guide the programs in preventive medicine, since the features of specific personality are related to differently to exposure to risk. - The treatment of the features and personality disorders could help to improve mental health and function, such as minimizing exposure to risk and the behaviors that jeopardize health.
Khemapech, Sansrimahachai, & Toahchoodee [6]	2016	They present a support system of ubiquitous nursing: UbiNurSS, which provides a wireless and dependable health alert and monitoring system. UbiNurSS comprises two subsystems, one which uses Raspberry Pi and the web application. Cardiac frequency and arterial pressure are the chosen vital signs for reflecting cardiovascular symptoms of the patient when compared against a range defined by nurses or doctors. A study about the use of text messages in the prevention of skin cancer.	- The results indicated that reading vital signs on a portable device is of added value through additional analysis for providing warnings in real time. - UbiNurSS functions correctly. However, one of the main inconveniences is the limited range of communication between the portable device and the Raspberry Pi; from 5.40 m to 13.50 m.
Bernabé, Cralle, & Gilbert [42]	2018	They present a review of various focuses of P4 medicine, including the wide-ranging studies of microbiota to understand the role of the human microbiota in health and illness, with a focus on preventive medicine.	- The results show that the application of the Systems Biology framework to the medical microbiota studies is still in its origins; there are substantial gaps in the knowledge with respect to what these associations represent in reality.

right medication for the specific disease affecting a specific person [65]. The use of personalized medicine will make clinical trials more efficient in reducing the costs that would arise due to adverse drug effects and prescription of medication that have been proven ineffective in certain genotypes [66].

Through personalized medicine the patient can receive an early monitoring of the signs and symptoms of any illness receive a preventive treatment that has benefitted other patients like him or her or have a treatment adapted to their characteristics.

The dynamic focuses based on P4 medicine will enable scientists and healthcare professionals to find better treatment objectives for various types of complex illnesses at different stages [67]. An important step in such efforts would be the discovery of dynamic biomarkers and based on systems for opportune alerts for pre-symptomatic diagnosis and prognosis to support the prediction and prevention of illnesses during different phases. These biomarkers would be useful for diminishing the risks of appearance of illnesses and disability, which is key for preventive medicine in risk populations [68].

**Table 5** Studies related to personalized medicine in telemedicine and ehealth

Authors	Year of publication	Study proposal	Results
Boland et al. [52]	2013	They present a study of the individual manifestations of innumerable diseases through electronic health records (EHR), called “EHR phenotyping”.	<ul style="list-style-type: none"> <li>- Define a new term: verotype, to group patients who have the same genotype, phenotype and subtype of clinical disease and develop personalized medical treatment regimens.</li> <li>- Describe the potential of a network-based approach to reverse engineer subtypes of clinical diseases through the use of EHR markers.</li> </ul>
McClellan et al. [53]	2013	They present a case study of breast cancer genetic risk prediction models. They describe how the use of individual genetic information in taking medical decisions could lead to inequalities capable of perpetuating disparities in the access to healthcare.	<ul style="list-style-type: none"> <li>- Since an ever-increasing number of medical decisions are based on individual genetic information, the potential for inequities that come about from the medical use of this information also increases and it is important to consider this possibility.</li> <li>- They suggest that the possibility of unequal access occurring along the continuum be recognized, from inequality that could be tolerated in different degrees up to intolerable, which could possibly equate to discrimination.</li> </ul>
Antoñanzas, Juárez-Castelló, & Rodríguez-Ibeas [54]	2015	They present a model for analyzing the decision that health authorities face when they must decide about the implementation of personalized medicine in a context of uncertainty. Genetic tests enable the stratification of the patient population, and medical research provides information about treatments.	<ul style="list-style-type: none"> <li>- They have combined both elements into a simple framework for analyzing decision making in personalized medicine.</li> <li>- The results point to the importance of having high-quality genetic tests to hand to classify patients. The calculated health benefits expected with the information provided by the test play an important role in the decision.</li> </ul>
Anaya et al. [55]	2016	They describe the gap between personalized medicine and its processes that can be offered to those healthcare systems with limited resources in illnesses such as rheumatoid arthritis (RA) and type 1 diabetes (T1D).	<ul style="list-style-type: none"> <li>- Personalized medicine predicts better results and a better trust and management of healthcare within any healthcare system by providing better predictions of results for scientists and healthcare professionals.</li> </ul>
Estape, Mays, & Sternke [56]	2016	They analyze the concept of personalized medicine in terms of: big data availability and the role of biomedical information in personalized medicine; the need for interdisciplinary teams in the development and evaluation of personalized treatment focuses; and the impact of electronic medical registry systems and clinical data storage in the field of personalized medicine.	<ul style="list-style-type: none"> <li>- The results show a general vision of the ethical worries related to personalized medicine and equity in health.</li> </ul>
Agapito, Guzzi, & Cannataro [57]	2018	They present the design and experimentation for a complete line of software, called microPipe, for the processing, notation and analysis of the data of the genotype of the single nucleotide polymorphism (SNP) based on micromatrices.	<ul style="list-style-type: none"> <li>- The main advantages of using microPipe are: the reduction of errors that can occur when trying to make data compatible between different tools; the possibility for analyzing in parallel enormous datasets; and the easy annotation and integration of data.</li> <li>- The effectiveness of microPipe for backing up personalized medicine is mainly related to its ability, in pharmacological studies, to find correlations between the individual’s genotype and the response to medication.</li> </ul>
Berrouiguet et al. [58]	2018	They present a new iHealth model from eHealth, for clinical evaluation and psychiatric treatment based on the incorporation of new technologies to clinical practices in order to improve self-control in real time, the extension of the evaluation of the patient’s environment and the processing of data using data mining to support medical decision making and personalized medicine.	<ul style="list-style-type: none"> <li>- The results of the study show that despite the challenges and limitations, iHealth can improve clinically-integrated decision making tools and the practice of personalized medicine, adapting the medical treatment to each patient.</li> <li>- Regarding the base for the advances in the evaluation of mental health that eHealth offers, iHealth will provide personalized clinical information out of the clinical views and the integration of multimodal data in real time of patients and carers using data extraction technology.</li> </ul>

Generally, in conclusion, P4 medicine will improve healthcare, will reduce the cost of healthcare and will stimulate the innovation and creation of new enterprises.

Therefore we propose several future lines: the development of 4P medicine systems in different specialties, propose cost-benefit analysis of the systems implemented and make public administrations aware of the importance of these systems in health in order to offer programs of financing for this type of development of P4 medicine systems.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

## References

- Jenkins, S. L., and Maayan, A., Systems pharmacology meets predictive, preventive, personalized and participatory medicine. *Pharmacogenomics* 14(2):119–122, 2013.
- Khoury, M. J., Gwinn, M., Glasgow, R. E., and Kramer, B. S. A., Population perspective on how personalized medicine can improve health. *Am. J. Prev. Med.* 42(6):639–645, 2012.
- Maier, M., Takano, T., and Sapir-Pichhadze, R., Changing paradigms in the management of rejection in kidney transplantation: Evolving from protocol-based care to the era of P4 medicine. *Can. J. Kidney Health Dis.* 4, 2017.
- Pravettoni, G., and Gorini, A., A P5 cancer medicine approach: Why personalized medicine cannot ignore psychology. *J. Eval. Clin. Pract.* 17(4):594–596, 2011.
- Hood, L., and Friend, S. H., Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat. Rev. Clin. Oncol.* 8(3):184–187, 2011.
- Khemapech, I., Sansrimahachai, W., and Toahchoodee, M., A real-time Health Monitoring and warning system for bridge structures. *Proceeding of IEEE Reg 10 Annu Int Conf/TENCON.* 3010–3033, 2016.
- Sabra, S., Alobaidi, M., Malik, K. M., and Sabeeh, V., Performance evaluation for semantic-based risk factors extraction from clinical narratives. *Proceeding of IEEE 8th Annu Comput Commun Work Conf CCWC.* 695–701, 2018.
- Green, S., and Vogt, H., Personalizing medicine: Disease prevention in silico and in socio. *HumanaMente J. Philos. Stud* 90(30):105–145, 2016.
- Pulciani, S., Di Lonardo, A., Fagnani, C., and Taruscio, D., P4 medicine versus Hippocrates. *Ann. Ist. Super. Sanità* 53(3):185–191, 2017.
- Ahmed, M. N., Toor, A. S., O’Neil, K., and Friedland, D., Cognitive computing and the future of health care cognitive computing and the future of healthcare: The cognitive power of IBM Watson has the potential to transform global personalized medicine. *IEEE Pulse* 8(3):4–9, 2017.
- Vogt, H., Hofmann, B., and Getz, L., The new holism: P4 systems medicine and the medicalization of health and life itself. *Med. Health Care Philos.* 19(2):307–323, 2016.
- Talukder, A. K., Chaitanya, M., Arnold, D., and Sakurai, K., Proof of disease: A blockchain consensus protocol for accurate medical decisions and reducing the disease burden. *Proceeding of IEEE SmartWorld, Ubiquitous Intell Comput Adv Trust Comput Scalable Comput Commun Cloud Big Data Comput Internet People Smart City Innov SmartWorld/UIC/ATC/ScalCom/CBDCom/IoP/SCI.* 257–262, 2018.
- Zhang, Y., Cheng, Y., Jia, K., and Zhang, A., Opportunities for computational techniques for multi-omics integrated personalized medicine. *Tsinghua Sci. Technol.* 19(6):545–558, 2014.
- Hood, L., and Flores, M., A personal view on systems medicine and the emergence of proactive P4 medicine: Predictive, preventive, personalized and participatory. *New Biotechnol.* 29(6):613–624, 2012.
- Sobradillo, P., Pozo, F., and Agustí, Á., P4 medicine: The future around the corner. *Arch. Bronconeumol.* 47(1):35–40, 2011.
- Noell, G., Faner, R., and Agustí, A., From systems biology to p4 medicine: Applications in respiratory medicine. *Eur. Respir. Rev.* 27(147):1–15, 2018.
- Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A. et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ.* 339, 2009.
- Poon, C. C. Y., Wang, M. D., Bonato, P., and Fenstermacher, D. A., Special issue on health informatics and personalized medicine. *Proceeding of IEEE Trans Biomed Eng.* 60(1):143–146, 2013.
- Hood, L., and Tian, Q., Systems approaches to biology and disease enable translational systems medicine. *Genomics Proteomics Bioinformatics* 10(4):181–185, 2012.
- Bengochea, J. A., Infection systems biology: From reactive to proactive (P4) medicine. *Int. Microbiol.* 15(2):55–60, 2012.
- Persch, A. C., Braveman, B. H., and Metzler, C. A., P4 medicine and pediatric occupational therapy. *Am. J. Occup. Ther.* 67(4):383–388, 2013.
- Shapira, N., Women’s higher health risks in the obesogenic environment: A gender nutrition approach to metabolic dimorphism with predictive, preventive, and personalized medicine. *EPMA J.* 4(1):1, 2013.
- Wegener, D., Rossi, S., Buffa, F., Delorenzi, M., and Rüping, S., Towards an environment for data mining based analysis processes in bioinformatics and personalized medicine. *Netw Model Anal Heal Informatics Bioinforma* 2(1):29–44, 2013.
- Miralles, F., Gomez-Cabrero, D., Lluch-Ariet, M., Tegnér, J., Cascante, M., and Roca, J., Predictive medicine: Outcomes, challenges and opportunities in the synergy-COPD project. *J. Transl. Med.* 12(2):S12, 2014.
- Bresó, A., Sáez, C., Vicente, J., Larrinaga, F., Robles, M., and García-Gómez, J. M., Knowledge-based personal health system to empower outpatients of diabetes mellitus by means of P4 medicine. *Human. In: Data Mining in Clinical Medicine.* 237–257, 2015.
- Guzzi, P. H., Agapito, G., Milano, M., and Cannataro, M., Methodologies and experimental platforms for generating and analysing microarray and mass spectrometry-based omics data to support P4 medicine. *Brief. Bioinform.* 17(4):553–561, 2016.
- Kodrič, K., Čamernik, K., Černe, D., Komadina, R., and Marc, J., P4 medicine and osteoporosis: A systematic review. *Wien. Klin. Wochenschr.* 128(7):480–491, 2016.
- Vogt, H., Hofmann, B., and Getz, L., Personalized medicine: Evidence of normativity in its quantitative definition of health. *Theor. Med. Bioeth.* 37(5):401–416, 2016.
- Mořa, M., Prevention of diabetes and 4P medicine. *Rom J Diabetes Nutr Metab Dis.* 24(1):7–12, 2017.

30. Sagner, M., McNeil, A., Puska, P., Auffray, C., Price, N. D., Hood, L. et al., The P4 health Spectrum – A predictive, preventive, personalized and participatory continuum for promoting Healthspan. *Prog. Cardiovasc. Dis.* 59(5):506–521, 2017.
31. Trovato, G. M., Behavior, nutrition and lifestyle in a comprehensive health and disease paradigm: Skills and knowledge for a predictive, preventive and personalized medicine. *EPMA J.* 3(1):8, 2012.
32. Younesi, E., and Hofmann-Apitius, M., From integrative disease modeling to predictive, preventive, personalized and participatory (P4) medicine. *EPMA J.* 4(1):23, 2013.
33. Simon, R., Clinical trials for predictive medicine: New challenges and paradigms. *Clin. Trials* 7(5):516–524, 2010.
34. Wang, F.-Y., and Wong, P. K., Intelligent systems and Technology for Integrative and Predictive Medicine: An ACP approach. *ACM Trans. Intell. Syst. Technol.* 4(2):1–6, 2013.
35. Pham, T., Tran, T., Phung, D., and Venkatesh, S., Predicting healthcare trajectories from medical records: A deep learning approach. *J. Biomed. Inform.* 69:218–229, 2017.
36. Tuck, M. G., Alemi, F., Shortle, J. F., Avramovic, S., and Hesdorffer, C., A comprehensive index for predicting risk of Anemia from patients' diagnoses. *Big Data* 5(1):42–52, 2017.
37. Swan, M., Health 2050: The realization of personalized medicine through crowdsourcing, the quantified self, and the participatory biocitizen. *J. Pers. Med.* 2(3):93–118, 2012.
38. Filipova-Neumann, L., and Hoy, M., Managing genetic tests, surveillance, and preventive medicine under a public health insurance system. *J. Health Econ.* 34(1):31–41, 2014.
39. Finch, L., Youl, P., Marshall, A. L., Soyer, H. P., Baade, P., and Janda, M., User preferences for text message-delivered skin cancer prevention and early detection. *J. Telemed. Telecare* 21(4):227–234, 2015.
40. Nohara, Y., Kai, E., Ghosh, P. P., Islam, R., Ahmed, A., Kuroda, M. et al., Health checkup and telemedical intervention program for preventive medicine in developing countries: Verification study. *J. Med. Internet Res.* 17(1):e2, 2015.
41. Hengartner, M. P., Kawohl, W., Haker, H., Rössler, W., and Ajdacic-Gross, V., Big five personality traits may inform public health policy and preventive medicine: Evidence from a cross-sectional and a prospective longitudinal epidemiologic study in a Swiss community. *J. Psychosom. Res.* 84:44–51, 2016.
42. Bernabé, B. P., Cralle, L., and Gilbert, J. A., Systems biology of the human microbiome. *Curr. Opin. Biotechnol.* 51:146–153, 2018.
43. O'Donnell, J. C., Personalized medicine and the role of health economics and outcomes research: Issues, applications, emerging trends, and future research. *Value Health* 16(6):S1–S3, 2013.
44. Evers, A. W., Rovers, M. M., Kremer, J. A., Veltman, J. A., Schalken, J. A., Bloem, B. R. et al., An integrated framework of personalized medicine: From individual genomes to participatory health care. *Croat Med J.* 53(4):301–303, 2012.
45. Ullman-Cullere, M. H., and Mathew, J. P., Emerging landscape of genomics in the electronic health record for personalized medicine. *Hum. Mutat.* 32(5):512–516, 2011.
46. Carlsten, C., Brauer, M., Brinkman, F., Brook, J., Daley, D., McNagny, K. et al., Genes, the environment and personalized medicine: We need to harness both environmental and genetic data to maximize personal and population health. *EMBO Rep.* 15(7):736–739, 2014.
47. Gwinn, M., and Khoury, M. J., Genomic, Personalized Medicine and Public Health. *Genomic and Personalized Medicine*. Elsevier Inc., 216–226, 2013.
48. Kouris, I., Tsimpas, C., Mougiakakou, S. G., Iliopoulou, D., and Koutsouris, D., E-health towards ecumenical framework for personalized medicine via Decision Support System. *Proceeding of 2010 Annu Int Conf IEEE Eng Med Biol Soc EMBC'10*. 2881–2885, 2010.
49. Weiss, S. T., Implementing personalized medicine in the academic health center. *J Pers Med.* 6(18), 2016.
50. Ginsburg, G. S., and Kuderer, N. M., Comparative effectiveness research, genomics-enabled personalized medicine, and rapid learning health care: A common bond. *J. Clin. Oncol.* 30(34):4233, 2012.
51. Vieta, E., Personalized medicine applied to mental health: Precision psychiatry. *Rev. Psiquiatr. Salud. Ment.* 8(3):117–118, 2015.
52. Boland, M. R., Hripcsak, G., Shen, Y., Chung, W. K., and Weng, C., Defining a comprehensive verotype using electronic health records for personalized medicine. *J. Am. Med. Inform. Assoc.* 20(e2):232–238, 2013.
53. McClellan, K. A., Avard, D., Simard, J., and Knoppers, B. M., Personalized medicine and access to health care: Potential for inequitable access? *Eur. J. Hum. Genet.* 21(2):143–147, 2013.
54. Antónanzas, F., Juárez-Castelló, C. A., and Rodríguez-Ibeas, R., Some economics on personalized and predictive medicine. *Eur. J. Health Econ.* 16(9):985–994, 2015.
55. Anaya, J. M., Duarte-Rey, C., Sarmiento-Monroy, J. C., Bardey, D., Castiblanco, J., and Rojas-Villarraga, A., Personalized medicine. Closing the gap between knowledge and clinical practice. *Autoimmun. Rev.* 15(8):833–842, 2016.
56. Estape, E. S., Mays, M. H., and Sterne, E. A., Translation in data mining to advance personalized medicine for health equity. *Intell. Inf. Manag.* 8(1):9–16, 2016.
57. Agapito, G., Guzzi, P., and Cannataro, M., A parallel software pipeline for DMET microarray genotyping data analysis. *High-Throughput.* 7(2):17, 2018.
58. Berrouiguet, S., Perez-Rodriguez, M. M., Larsen, M., Baca-García, E., Courtet, P., and Oquendo, M., From eHealth to iHealth: Transition to participatory and personalized medicine in mental health. *J. Med. Internet Res.* 20(1):e2, 2018.
59. Sagner, M., McNeil, A., and Arena, R., The Next Chapter: The Future of Health Care and Lifestyle Interventions. *Lifestyle Medicine: Lifestyle, the Environment and Preventive Medicine in Health and Disease*. Elsevier, 437–446, 2017.
60. Hood, L., and Auffray, C., Participatory medicine: A driving force for revolutionizing healthcare. *Genome Med.* 5(12):110, 2013.
61. Vasilateanu, A., Radu, I. C., and Buga, A., Environment crowdsensing for asthma management. *Proceeding of E-Health Bioeng Conf EHB.* 1–4, 2015.
62. Morley, J. E., and Anker, S. D., Myopenia and precision (P4) medicine. *J. Cachexia. Sarcopenia Muscle* 8(6):857–863, 2017.
63. Nikolaiev, S., and Timoshenko, Y., Reinvention of the cardiovascular diseases prevention and prediction due to ubiquitous convergence of mobile apps and machine learning. *Proceeding of 2015 Inf Technol Innov Bus Conf ITIB.* 23–26, 2015.
64. Biesecker, L. G., Hypothesis-generating research and predictive medicine. *Genome Res.* 23(7):1051–1053, 2013.
65. Gupta, P. D., Pharmacogenetics, pharmacogenomics and ayurgenomics for personalized medicine: A paradigm shift. *Indian J. Pharm. Sci.* 77(2):135–141, 2015.
66. Vilhelmsson, A., Value-based health care delivery, preventive medicine and the medicalization of public health. *Cureus* 9(3):10–13, 2017.
67. Hood, L., Systems biology and P4 medicine: Past, present, and future. *Rambam Maimonides Med J.* 4(2), 2013.
68. Yan, Q. Systems and dynamical medicine: The roles of translational bioinformatics. In: *Translational Bioinformatics and Systems Biology Methods for Personalized Medicine*. 13–24, 2017.

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