Ann Ist Super Sanità 2017 | Vol. 53, No. 3: 185-191
DOI: 10.4415/ANN_17_03_02

P4 Medicine *versus* Hippocrates

Simonetta Pulciani[1], Anna Di Lonardo[2], Corrado Fagnani[3] and Domenica Taruscio[1]

[1]*Centro Nazionale Malattie Rare, Istituto Superiore di Sanità, Rome, Italy*
[2]*Dipartimento Malattie Cardiovascolari, Dismetaboliche e dell'Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
[3]*Centro Scienze Comportamentali e Salute Mentale, Istituto Superiore di Sanità, Rome, Italy*

Abstract
Hippocrates was the first to raise awareness of medicine as a science. He asserted the body being a unified whole and emphasized the importance of preventive and predictive medicine, spurring physicians to foster patient collaboration. Recent achievements today have permitted a new approach "P4 medicine" – Predictive, Preventive, Personalized and Participatory – with the aim of depicting an individual's health history and molecular profile in determining the best medical intervention in maintaining or restoring wellbeing. There is a link, which brings together Hippocrates and P4 Medicine. This review will elaborate further this statement, considering the scientific achievements that paved the way for recent medical approaches. Emphasis will be given to the social impact of new diagnostic and therapeutic protocols, considering their costs and their success probabilities.

Key words
- Human Genome Project
- history of medicine
- participatory medicine
- computational biology

INTRODUCTION

Hippocrates was the first to assert that diseases are derived from natural causes and raised the awareness of medicine being a science and underlined its historical development [1-5]. The Greek scientist considered medicine a union between theory and practice, and stated "Medicine had already fulfilled important achievements, and acquired all the premises for going further, always considering the discoveries already done and moving from them".

Since Hippocrates, medical sciences have come down a long path to the present day sequencing of the complete human genome, as defined by the scientist F.S. Collins, a revolution in the biomedical sciences, "Gene isolation provides the best hope for understanding human disease at its most fundamental level… Knowledge about genetic control of cellular functions will underpin future strategies to prevent or treat disease phenotypes" [6-9].

The astounding project of human genome sequencing would not have been possible without past scientific discoveries, such as the Mendel's laws and their application in the analysis of human inborn errors of metabolism, as investigated by Garrod, the elucidation of the double-helical structure of DNA, the genetic code, and the implementation of recombinant DNA technology [7]. In the future, the analysis and characterization of human sequences and the cross-referencing of species may make it possible to understand the biological structure and function of many genes and to construct cellular pathways in healthy and diseased cells. Collins foresaw "obtaining the sequence of the human genome is the end of the beginning" [8, 10, 11].

The past and the future of the Human Genome Project confirm that biomedical research is like a long chain, and each link represents a new achievement connected to the previous one, just as Hippocrates had suggested "going further, always considering the discoveries already done and moving from them" [6-10].

In the post genomic era[1], the accomplishment of the Human Genome Project and the modern "omics" technologies are providing new directions in medical approaches, and P4 Medicine appears to be the acme of the new perspectives [12-14], aiming to redefine medical intervention. As defined by the Predictive, Preventive, Personalized "Ps", medical interventions must be tailored considering the medical, genetic and personal data of each individual [15-17]. While, the Participatory "P" hopes and calls for the active involvement of patients [18]. These perspectives of P4 Medicine recall Hippocrates' thoughts "the human body as one unified organism to be considered as one coherent and integrated whole, and the disease symptoms should be analyzed and evaluated considering the environment and

[1]The term "the post genomic era" highlights the current period of time that follows the Human Genome Project achievement. The same period of time can be also identified with the term "genomic era". We have selected and used the term "post genomic era" to clearly underline the Human Genome Project accomplishment, and the start of a new scientific era committed to characterize genes' functions, regulation and interactions.

Address for correspondence: Simonetta Pulciani, Centro Nazionale Malattie Rare, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: simonetta.pulciani@iss.it.

social status of the patients", and "the best physician is the one who can prevent and predict" [1-5].

The medical sciences have come down a long path from Hippocrates; still, his recommendations for pursuing a correct and suitable therapeutic regime now appear in the post genomic approach of 4P Medicine.

P4 MEDICINE

The achievements of the Human Genome Project and "omics" technologies have given new impetus to Science [6-10]. Today, the information derived from this project can be considered akin to a huge book that is to be wisely read and interpreted to unravel the genes structure and hierarchy, this being the principal goal of the post genomic era [8]. This achievement will not be simple to attain. Researchers of diverse disciplines have come together with their expertise in the effort to pursue and reach this compelling result that, in the end, will permit the understanding of the mechanisms underlying the regulation or deregulation of disease-associated genes. Biologists, mathematicians, chemists and engineers are all collaborating to set up new protocols and instruments dedicated in performing a wide range analysis of DNA, RNA and proteins with even the use of compelling methods [13, 19]. An example, the evolution of instruments for synthesizing, detecting, and sequencing DNA has permitted the reading of a human genome in a short time and at a reasonable cost, making the analysis of polymorphisms and gene alterations more and more viable. Nowadays, it is possible to sequence the whole human genome in about three days, and for less than € 3000. However, the new technologies are improving at a fast rate, shortening the sequencing time and the costs becoming more affordable each day [19]. RNA and protein Microarrays are providing suitable information to decipher the molecular mechanisms of gene transcriptions and translation [20, 21]. Moreover, mathematicians are contributing to the post genomic challenges by developing modern computational tools capable of analyzing a multitude of data acquired via these new sophisticated protocols [22]. The new "omics" technosciences, such as genomics, proteomics, metabolomics and interactomics, have the objective to interpret and organize this huge amount of results, to ultimately design molecular networks and pathways. In the future, these "omics" profiles may be used as tools for the better prevention, diagnosis, and treatment of diseases. In fact, the molecular data will be a determinant in improving diagnostic and therapeutic strategies when personal and life style information is considered [23].

Besides this, the new platforms of communication are revolutionizing the access to medical information for patients and their families, favoring their active participation in decision making of their own health, aided by the Internet [24].

More than a decade ago, Leroy Hood explored all these potentialities and proposed the Predictive, Preventive, Personalized and Participatory medicine, known today as P4 Medicine. Leroy Hood put forward this concept with the objective of changing medical intervention from the care of the diseases to the maintenance of wellbeing [25-27].

This approach aspires to define and explore healthy and altered molecular profiles to predict the health course of individuals, considering their unique genetic and epigenetic background embedded in their specific social and physical environments.

The molecular parameters, integrated with the medical histories of patients and their health outcomes derived from the common clinical observations, will give some insight into disease outcomes and how these affect the physiological status of the individual.

Combining the molecular, clinical and personal data together, it would be possible to define genetic variants along with molecular pathways related to status of wellness and sickness. This could highlight the potential alterations correlated in disease onset. The dynamics of perturbed molecular profiles will potentially predict the emergence of illness; therefore, it may help to select personalized interventions directed to prevent or eventually cure diseases and to restore the wellness status. These interventions will focus on both suitable drugs and appropriate life style changes [26-28].

An extensive implementation of "omics" technosciences and of computational tools is fundamental in collecting and assembling the appropriate data, but it is not enough. Even though the P4 approach is based on the analysis of molecular, phenotypic and lifestyle data of each individual, this personal data will be correctly interpreted only if collected by benchmark procedures and compared with similar data of other patients [26-28]. Comparative studies will define the best methods of sample preparation and the most suitable algorithms to design unbiased molecular patterns. Finally, these comparisons will highlight the molecular variations that are relevant in maintaining or losing the well-being status. This selection and discernment of the relevant data will clearly define the health molecular networks of each individual, and by scoring their fluctuation it will be possible to predict illness outcome and to plan prevention strategies or therapeutic interventions. These comparative studies require a broad access to personal datasets of patients and the creation of linkages among these. Hence, scientists are faced with the challenge of acquiring, sharing, protecting these data, together with all the resulting ethical problems, such as storage and management, encouraging patients to give access to their personal and medical information. Additionally, physicians and other members of the medical community should master how to share their information, scientific knowledge and objectives with patients [29, 30]. Patients must be made aware that their, clinical, molecular, phenotypic data and life-style are fundamental for the advancement of knowledge, as this will increase their willingness to provide access to their personal data. In fact, this conscious patient participation is the purpose of the Participatory "P" and is mandatory in moving toward the P4 approach; however, there is the likelihood that this will be the hardest goal to achieve.

P4 MEDICINE *VERSUS* HIPPOCRATES

The scientist Leroy Hood has launched P4 Medicine in exploring and exploiting the knowledge and technologies derived from the Human Genome Project.

He has introduced the P4 approach with the intent to potentiate prevention as the main component of medical care. The scientist explains that the "omics" molecular data and the new computational tools can favor and support this concept, shifting medical intervention from the care of the diseases to the maintenance of wellbeing [16].

Although P4 Medicine appears to be a modern science taking into consideration the knowledge and the "omics" technologies, of which it is based on. Reviewing this in depth, one perceives that its premises and purposes actually echo the thoughts of the ancient Greek physicist Hippocrates.

Hippocrates had been the first to deny that diseases were derived from the curse of the gods and introduced the concept of medicine as science. Indeed, he emphasized "Medicine has acquired all the premises for going further, always considering the discoveries already done and moving from them". For these reasons, Hippocrates is claimed to be the "father of medicine", and this soubriquet acquires even more relevance when comparing his ideas with the P4 Medicine approach [3, 31].

In fact, the Greek physician founded his method on the concept that the human body functioned as one unified organism, a coherent and integrated whole, embedded in its own physical and social environment. Hippocrates believed in the continuity between health and disease. He perceived diseases as a succession of regulated phenomena that were bonded together and advised "diseases never affect only one part of the body, they affect the health balance of all body". Additionally, Hippocrates encouraged physicians to analyse symptoms to interpret the present trends of the disease and to predict its development relative to the past health history of the patient. His approach intends to examine and analyse the present and past health conditions to focus on their possible future development. In this regard, the ancient scientist stressed "He who administers therapy must first know the whole man as a unique psychosomatic entity in relation to his social and natural environment" [1-5].

The Greek physician pointed out the importance of geography, climate and hydrological environment as main determinants that, besides nutrition and hygiene, could condition the onset of diseases and their development. He underlined that the social environment, as well as working and living conditions may influence the psychology and personal feeling relative to the illness, and may have a significant relevance for the disease outcome and development. In this respect, Hippocrates proclaimed "The best physician is who can prevent and predict diseases", and spurred his pupils to achieve this objective by investigating "the entire patient and his environment" [5, 31].

Marketos had clearly explained "He observed diseases with the eye of a naturalist and established rules by which the physician would know what to expect and what to do at the right time. Every patient was a separate case and this individuality precludes a fixed dogma for curative methods. Hippocrates and his disciples collected scientific case histories as no-one had done previously; for example in *Epidemics* he described the events of illness with cool detachment and in a truly scientific way he declared: *State the past, diagnose the present and foretell the future*" [3, 4]. According to Hippocrates, the past and the present can provide the proper knowledge to prognosticate the future, thought that brought a revolution in Medicine and all Sciences [2]. Hence, Hippocrates' ideals of good medical practice relied on the holistic view of the human body, examined relative to the past and present health history and life style of every individual, to better prevent, predict and cure illnesses.

This can be said to be true, as the thoughts of the ancient scientist parallel the premises of the P4 Medicine of today, in aiming to protect the wellness status of individuals by analysing and comparing their personal and clinical data.

P4 Medicine exploits two thousand years of scientific achievements and the latest molecular and computational achievements *(Table 1)* [15]; however, the fundaments still echo Hippocrates' idea of a medicine founded on the examination of the patients as one whole taking into account their physical, social and psychological status. This statement is even more valid when considering the role of patients along the therapeutic path.

Hippocrates strongly advised physicians to focus their attention on the patient as well as on the disease, stressing the importance of the relationship between physician and patient. According to Hippocrates, the Art of medicine has three Actors, the disease, the patient and the physician; the physician is the "Art Master", and should fight the diseases together with the patient. The Greek scientist encouraged the physician to provide the patient the education for the healing process, helping the patient to understand oneself and the disease, making the patient a protagonist in fighting the disease [1-5]. Furthermore, in his first aphorism "Life is short, and Art is long", Hippocrates highlights the brevity of human life and the improbability for physicians to acquire all the necessary knowledge about any disease they may encounter. The Greek scientist warned physicians to be aware when treating diseases that they may not always have adequate and appropriate expertise in achieving a correct diagnosis and cure. To overcome this disadvantage, Hippocrates advised medical practitioners to harvest information from their patients and other stakeholders which would fill the knowledge voids and prevent other failures [5, 32]. In reality, this aphorism gave rise to Participatory medicine long before the advent of P4 Medicine [18].

Even if at first sight, Hippocrates, P4 medicine and the Human Genome Project appear as far apart as the years that separate them, they are intrinsically tied when considering the ancient reasoning and the rationale behind the modern scientific achievements and their future perspectives [1-5, 18]. Furthermore, the will to educate the patient about his disease to foster his active collaboration to combat the illness brings the ancient scientist and the modern approach that much closer. Hippocrates and Leroy Hood both hoped for a proactive medicine mainly directed in predicting and preventing illness more than curing it, and underlines the crucial role of an informed and collaborative pa-

Table 1
Relevant molecular biology achievements from '800 up to the Human Genome Project

Year	Main achievements	Scientists
1865	Hybridization of pea plants	G. Mendel
1869	Localization of DNA in the nucleus and named "nucleic acid"	F. Miescher
1885	Hypothesizing of chromosomes as the inheritance carriers	W. Roux
1902	Formulation of heredity chromosomal theory	W. Sutton
1914	Localization of genes on chromosomes	T. Morgan C. Bridges
1944	Hypothesis of genes being made up of DNA	O. Avery C. Mcleod M. McCarty
1944	The book *What is life?* suggesting complex molecules as carriers of genetic code for living organisms	E. Schrödinger
1953	The proposing of double-stranded, helical, complementary, anti-parallel model for DNA	J. Watson F. Crick
1959	Discovered of "operon"	F. Jacob J. Monod
1961	Determination of "genetic code"	M. Nirenberg H. Mathaei S. Ochoa
1961	Discovery of messenger RNA	S. Brenner F. Jacob M. Meselson
1966	Finalization of genetic code	M. Nirenberg H. Gobind Khorana
1970	Discovered reverse transcriptase	H. Temin D. Baltimore
1972	*In vitro* first recombination of DNA	P. Berg
1973	Plasmid to clone DNA	H. Boyer S. Cohen
1976	Development of Southern Blot technique	E. Southern
1977	Development of the DNA sequencing technique	W. Gilbert F. Sanger
1983	Development of polymerase chain reaction (PCR)	K. Mullis
1990	Development of the Human Genome Project	Various research groups
1990	Introduction of BLAST, "fast sequence similarity searching tool"	S. Karlin S.F. Altshul
1991	Introduction of EST, "expressed sequence tag sequencing"	J.C. Venter *et al.*
1996	Development of microarrays	P. Brown
2001	The announcement of the human genome draft version (3200 Mb)	F.S. Collins J.C. Venter
2002	Final presentation of human genome	F.S. Collins J.C. Venter

tient. The physicians must create a deep collaborative relationship with patients and give them clear and adequate information about their health status, since a more participative patient will contribute positively to the therapeutic path. A good relationship will facilitate the exchange and comprehension of medical information, will permit a better identification of the patient needs, and will help to contain patient fears. A good communication will encourage the patient to share more personal and illness information, and therefore it may allow a better and faster diagnosis, thus playing unarguably a more positive role in health care decisions.

P4 MEDICINE ETHICAL, SOCIAL AND ECONOMIC IMPLICATIONS AND HIPPOCRATES

P4 Medicine is still far from being accomplished, as it already poses several issues that need to be addressed

and resolved [33]; once more Hippocrates has paved the corrected route for us to follow [1, 4, 31].

Hippocrates teaching is founded on the sacred respect of the patient; this being the necessary prerequisite to face and to overcome the huge challenges and contradictions of the post genomic medicine [1, 31, 33].

This medical approach aims to maintain the wellness status by exploiting the knowledge of genetic maps, molecular pathways and health strategies built up by the systematic analysis of millions of records, from millions of individuals and patients, invited to share their personal information. These premises raise many ethical challenges that need to be faced [33]. Among these, the correct sharing, storage and use of personal information are important issues to be met to guarantee the privacy of patients and, therefore, their willingness and acceptance to disclose their own data [29, 33]. Hippocrates' oath states "Whatever I may say or hear in the course of a treatment, or even unrelated to treatment, in regard to the lives of men that should not be spoken of abroad, I will keep to myself, holding such things in confidence" [34], underlining the physician's responsibility of caring and protecting lives and feelings of patients.

Additionally, most of these data will be based on new diagnostic approaches derived from the Human Genome Project and "omics" technologies. These procedures are extremely complex and expensive; therefore, they are not easily available and affordable [35, 36] to everyone.

The high costs could generate a type of "financial discrimination" of people who can or cannot undertake the most appropriate diagnostic path. This consideration highlights that "omics" approaches could lead to an inequitable medicine. Additionally, relevant "omics" data could be absent due to this financial aspect could generate holes in the computational system, and this may compromise the right interpretation of genotypes and metabolic pathways [17, 35, 36].

Hence, it would be desirable to add a new "P" to P4 Medicine, namely, a "P" for "People" Medicine to overcome any computational bias and social discrimination, as Hippocrates had sworn to Apollo "for the benefit of my patients and protect them from harm and injustice" [34].

Some scientists have already added the "P5" of Psycho-cognitive medicine [37-39] and the "P6" of Public and Population-based medicine [40]. The "P5" underlines that psycho-cognitive attitudes of each individual being unique and relevant for health outcome, as they may affect therapeutic choices, influence the physician-patient relationship and, in the end, determine how individuals prevent and cope with diseases.

Undoubtedly, the P5 fully accomplishes the Hippocrates' concept that each individual should be considered as a unique psychosomatic entity [1-5, 38]. The "P6" summarizes the Cumming's idea, "Healthcare of the future thus becomes P4 + Cn where C represents community, collaboration, self-caring, co-creation, co-production, and co-development using technologies delivered via the Internet" [41]. This "P6" concept was derived from Salvatore Iaconesi's experience of sharing his illness on the public domain, in asking for help and consideration.

In fact, the new proposed "P" of People Medicine also includes most of the "C" of Cumming's idea of P4 + Cn, but it tries to go further in avoiding discrimination. This goal is very difficult to achieve, considering that nowadays a large part of the world population does not have access to basic health care, and thus it would be pure fiction to have "omics" diagnostic and therapeutic paths included for this population [35].

Medicine should be for People, where wellbeing is a legitimate expectation of every person regardless of social status. Yet, this appears not to be the case [42, 43]. Biomedical research requires enormous financial resources and its tools cannot be supplied gratis. However, these should be made more affordable and widely available. Individuals should never have to give up the hope of benefiting from the best diagnostic and therapeutic approaches [43].

It needs to be stressed that, as P4 medicine and its "omics" protocols are in their infancy, and most of their applications still need to be harmonized, they cannot always provide what is expected of them. Hence, the "omics" approach of P4 Medicine could delude and disappoint patients who have high expectations related to the prediction, prevention and cure of diseases [35, 44].

As the "omics" will generate more knowledge on the mechanisms of gene regulation, transcription and translation, as well as proteins interactions, P4 Medicine is expected to increasingly pursue effectively its tasks and to guarantee a better health outcome. It again needs to be stressed that this goal can only be achieved through the analysis of huge amounts of "omics" data (genomic, transcriptomic, metabolomic, proteomic and so on), obtained without any financial bias. Together, these unbiased data may provide the right information to improve the knowledge of physiological and pathological pathways and to configure the appropriate therapeutic strategies. This requires implementing the "P" of People Medicine, so that a majority of individuals can be involved and included in "omics" screenings.

CONCLUSIONS

P4 Medicine and Hippocrates are centuries apart, yet their concepts of best therapeutic approaches are very similar. P4 Medicine is based on omics techno-science and demands patients actively participate in medical decisions to guide the necessary changes in fully achieving their goals. Hippocrates considered the body as a unified whole and a unique psychosomatic entity, and based his method on the analysis of symptoms and how these were affected by natural and social environments. Additionally, he underlined preventive and predictive medicine as the best therapeutic approach, and strengthened the importance of the alliance between physician and patient. Even, in the post genomic era the therapeutic alliance is going to be crucial for fulfilling the Participation and People requirements and demonstrating how care of individuals, and consideration for their needs are still the first and most important steps to accomplishing great achievements. These "Ps" will also reinforce the alliance between patient and physician, and lead to a "human omics medicine", which bonds together scientific achievements and compassion, and

is able to face illness and cope with distress, according to Hippocrates ideal "Wherever the art of medicine is loved, there is also a love of humanity".

Authors' contribution statement

Simonetta Pulciani is the author of the manuscript, and Anna Di Lonardo, Corrado Fagnani, Domenica Taruscio revised the text.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments

Part of the work has been presented as an Abstract to The 11th Annual ICORD Meeting, 19-22 October 2016, Cape Town, South Africa.

The authors wish to thank Dr Franca Podo for the useful comments and Andrea Vittozzi for the technical support. We would finally like to thank Maurice Di Santolo for the English revision of the final draft.

Received on 28 November 2016.
Accepted on 15 May 2017.

REFERENCES

1. Lunshof JE, Chadwick R, Church GM. Hippocrates revisited? Old ideals and new realities *Genomic Med* 2008;2(1-2):1-3. DOI 10.1007/s11568-008-9020-2
2. Geymonat L. *Storia del pensiero filosofico e scientifico*. Vol. 1. Available from: https://unisafilosofiateoreticaonline.wordpress.com/supplementi/storia-del-pensiero-scientifico-e-filosofico-ludovico-geymonat/.
3. Marketos SG. *History of Medicine*. Available from: http://asclepieion.mpl.uoa.gr/parko/marketos2.htm.
4. Tsiompanou E, Marketos SG. Hippocrates: timeless still. *J R Soc Med* 2013;106(7):288-92. DOI: 10.1177/0141076813492945
5. *Hippocrates. Vol. I-VIII*. Annotated Greek text and English translation by Jones WHS, Withington ET, Potter P, Smith WD. The Loeb Classical Library. Cambrige Harvard University Press; London: W. Heinemann, London, 1923-1995.
6. Kellenberger E. The evolution of molecular biology. *EMBO Rep* 2004;5(6):546-9. DOI: 10.1038/sj.embor.7400180
7. Balmain A. Cancer genetics: from Boveri and Mendel to microarrays. *Nat Rev Canc* 2001;1:77-82. DOI: 10.1038/35094086
8. Collins FS. Medical and Societal Consequences of the Human Genome Project. *N Engl J Med* 1999;341(1):28-37. DOI: 10.1056/NEJM199907013410106
9. Gonzaga-Jauregui C, Lupski JR, Gibbs RA. Human genome sequencing in health and disease. *Ann Rev Med* 2012;63:35-61. DOI: 10.1146/annurev-med-051010-162644
10. Durmaz AA, Karaca E, Demkow U, Toruner G, Schoumans J, Cogulu O. Evolution of genetic techniques: past, present, and beyond. *Biomed Res Int* 2015;2015:461-524. DOI: 10.1155/2015/461524
11. Joyner MJ, Prendergast FG. Chasing Mendel: five questions for personalized medicine. *J Physiol* 2014;592(11):2381-8. DOI: 10.1113/jphysiol.2014.272336
12. Roden DM, Tyndale RF. Genomic medicine, precision medicine, personalized medicine: what's in a name? *Clin Pharmacol Ther* 2013;94(2):169-72. DOI: 10.1038/clpt.2013.101
13. Alyass A, Turcotte M, Meyre D. From big data analysis to personalized medicine for all: challenges and opportunities. *BMC Med Genomics* 2015;8:33. DOI: 10.1186/s12920-015-0108-y
14. Dudley JT, Listgarten J, Stegle O, Brenner SE, Parts L. Personalized medicine: from genotypes, molecular phenotypes and the quantified self, towards improved medicine. *Biocomputing* 2015:342-6. DOI. org/10.1142/9789814644730_0033
15. Hood L. Systems biology and p4 medicine: past, present, and future. *Rambam Maimonides Med J* 2013;4(2):e0012. DOI: 10.5041/RMMJ.10112
16. Schmidt C. Leroy Hood looks forward to P4 medicine: predictive, personalized, preventive, and participatory. *J Natl Cancer Inst* 2014;106(12). pii: dju416. DOI: 10.1093/jnci/dju416
17. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. *Per Med* 2013;0(6):565-76. DOI: 10.2217/PME.13.57
18. Hood L, Auffray C. Participatory medicine: a driving force for revolutionizing healthcare. *Genome Med* 2013;5(12):110. DOI: 10.1186/gm514
19. Shen T, Lee A, Shen C, Lin CJ. The long tail and rare disease research: the impact of next-generation sequencing for rare Mendelian disorders. *Genet Res (Camb)* 2015;97:e15. DOI: 10.1017/S0016672315000166
20. Hood L, Balling R, Auffray C. Revolutionizing medicine in the 21st century through systems approaches. *Biotechnol J* 2012;7(8):992-1001. DOI: 10.1002/biot.201100306
21. Marzancola MG, Sedighi A, Li PC. DNA Microarray-Based Diagnostics. *Methods Mol Biol* 2016;1368:161-78. DOI: 10.1007/978-1-4939-3136-1_12
22. Tenenbaum JD. Translational Bioinformatics: Past, Present, and Future. *Genet Prot Bioinform* 2016;14(1):31-41. DOI:10.1016/j.gpb.2016.01.003
23. A Moraes F, Góes A. decade of human genome project conclusion: Scientific diffusion about our genome knowledge. *Biochem Mol Biol Educ* 2016;44(3):215-23. DOI: 10.1002/bmb.20952
24. Glick M. The Internet-informed patient: opportunities for patient-centered care. *J Am Dent Assoc* 2013;144(3):239-40.
25. Sagner M, McNeil A, Puska P, Auffray C, Price ND, Hood L, Lavie CJ, Han ZG, Chen Z, Brahmachari SK, McEwen BS, Soares MB, Balling R, Epel E, Arena R. The P4 Health Spectrum. A predictive, preventive, personalized and participatory continuum for promoting healthspan. *Prog Cardiovasc Dis* 2016; pii: S0033-0620(16)30078-0. DOI: 10.1016/j.pcad.2016.08.002
26. Song M, Lee HW, Kang D. The potential application of personalized preventive research. *Jpn J Clin Oncol* 2014;44(11):1017-24. DOI: 10.1093/jjco/hyu135
27. Toga AW, Foster I, Kesselman C, Madduri R, Chard K, Deutsch EW, Price ND, Glusman G, Heavner BD, Dinov ID, Ames J, Van Horn J, Kramer R, Hood L. Big biomedical data as the key resource for discovery science. *J Am Med Inform Assoc* 2015;22(6):1126-31. DOI: 10.1093/jamia/ocv077
28. Budin-Ljøsne I, Harris JR. Ask not what personalized medicine can do for you--ask what you can do for person-

alized medicine. *Public Health Genomics* 2015;18(3):131-8. DOI: 10.1159/000373919
29. Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, Riess O, Straub V, Posada M, Taruscio D, Mascalzoni D. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. *Eur J Hum Genet* 2016;24(9):1248-54. DOI: 10.1038/ejhg.2016.2
30. Mittelstadt BD, Floridi L. The Ethics of Big Data: Current and foreseeable issues in biomedical contexts. *Sci Eng Ethics* 2016;22(2):303-41. DOI: 10.1007/s11948-015-9652-2
31. Chambers DW. A brief history of conflicting ideals in health care. *J Am Coll Dent* 2001;68(3):48-51.
32. Antoniou GA, Antoniou SA, Georgiadis GS, Antoniou AI. A contemporary perspective of the first aphorism of Hippocrates. *J Vasc Surg* 2012;56(3):866-8. DOI: 10.1016/j.jvs.2012.05.002
33. Brothers KB, Rothstein MA. Ethical, legal and social implications of incorporating personalized medicine into healthcare. *Per Med* 2015;12(1):43-51. DOI: 10.2217/pme.14.65
34. Emery AE. Hippocrates and the oath. *J Med Biogr* 2013;21(4):198-9. DOI: 10.1177/0967772013513395
35. Pulciani S, Vittozzi A, Diemoz S, Nutile E, Taruscio D. Le malattie rare nell'era post-genomica. *Prog Med* 2017;108(7):1-9.
36. Tursz T, Bernards R. Hurdles on the road to personalized medicine. *Mol Oncol* 2015;9(5):935-9. DOI: 10.1016/j.molonc.2014.08.009
37. Pravettoni G, Gorini A. A P5 cancer medicine approach: why personalized medicine cannot ignore psychology. *J Eval Clin Pract* 2011;17(4):594-6. DOI: 10.1111/j.1365-2753.2011.01709.x
38. Gorini A, Pravettoni G. P5 medicine: a plus for a personalized approach to oncology. *Nat Rev Clin Oncol* 2011;8(7):444. DOI: 10.1038/nrclinonc.2010.227-c1
39. Ozdemir V, Knoppers BM. One size does not fit all: toward "upstream ethics"? *Am J Bioeth* 2010;10(6):42-4. DOI: 10.1080/15265161.2010.482639
40. Bragazzi NL. From P0 to P6 medicine, a model of highly participatory, narrative, interactive, and 'augmented' medicine: some considerations on Salvatore Iaconesi's clinical story. *Patient Prefer Adherence* 2013;7:353-9. DOI: 10.2147/PPA.S38578
41. Cumming G, Fowlie A, McKendrick D, Hogg J, Brooks E, McClusky C, French T, Eckl C. H = P4 + C and Health Web Science: "A Hippocratic Revolution in Medicine". In: *Proceedings of the ACM WebSci '11 3rd International Conference on Web Science*. June 14-17, 2010; Koblenz, Germany. Available from: http://citeseerx.ist.psu.edu/viewdoc/download? DOI=10.1.1.462.3859&rep=rep1&type=pdf
42. Cohen JP, Felix AE. Personalized Medicine's Bottleneck: Diagnostic Test Evidence and Reimbursement. *J Pers Med* 2014;4(2):163-75. DOI: 10.3390/jpm4020163
43. Lewis J, Lipworth W, Kerridge I. Ethics, evidence and economics in the pursuit of "personalized medicine". *J Pers Med* 2014;4(2):137-46. DOI: 10.3390/jpm4020137
44. Christensen KD, Dukhovny D, Siebert U, Green RC. Assessing the costs and cost-effectiveness of genomic sequencing. *J Pers Med* 2015;10;5(4):470-86. DOI: 10.3390/jpm5040470