REVIEW ARTICLE

Precision medicine for managing chronic diseases

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KEY WORDS

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ABSTRACT

Precision medicine (PM) is an important modern paradigm for combining new types of metrics with big medical datasets to create prediction models for prevention, diagnosis, and specific therapy of chronic diseases. The aim of this paper was to differentiate PM from personalized medicine, to show potential benefits of PM for managing chronic diseases, and to define problems with implementation of PM into clinical practice. PM strategies in chronic airway diseases, diabetes, and cardiovascular diseases show that the key to developing PM is the addition of big datasets to the course of individually profiling diseases and patients. Integration of PM into clinical practice requires the reengineering of the health care infrastructure by incorporating necessary tools for clinicians and patients to enable data collection and analysis, interpretation of the results, as well as to facilitate treatment choices based on new understanding of biological pathways. The size of datasets and their large variability pose a considerable technical and statistical challenge. The potential benefits of using PM are as follows: 1) broader possibilities for physicians to use the achievements of genomics, proteomics, metabolomics, and other "omics" disciplines in routine clinical practice; 2) better understanding of the pathogenesis and epidemiology of diseases; 3) a revised approach to prevention, diagnosis, and treatment of chronic diseases; 4) better integration of electronic medical records as well as data from sensors and software applications in an interactive network of knowledge aimed at improving the modelling and testing of therapeutic and preventative strategies, stimulating further research, and spreading information to the general public.

Introduction Throughout centuries, medicine has evolved from Hippocrates' "humors" to a more pathophysiology-oriented interpretation of clinical phenomena, until the current "omic" sciences (eg, genomics, proteomics, or metabolomics). At present, we are entering an exciting period of medicine, where a convergence of genomics, bioinformatics, and new molecular techniques promises to improve our understanding of disease mechanism, preventing its onset and enabling early detection, as well as tailoring therapy to patient's characteristics. It is now clear that the "blockbuster approach" (ie, "one size fits all") can no longer be used as a paradigm of health care. The necessity for change has spawned the emergence of a new concept, namely, "precision medicine" (PM).

PM is a novel approach that can be characterized as molecular, immunologic, and functional endotyping of the disease, leading to personalized care, with the patient's engagement in decision making as to the treatment process and consideration of predictive and preventive aspects of treatment.[1] The aim of PM is the practical application of scientific results by using molecular, environmental, and behavioral biomarkers in redefining our understanding of the disease process and patient response.[2]

The term "precision medicine" was coined by Clayton Christensen from Harvard Business School in Boston, who used it in his book, *The Innovator's Prescription* (published in 2009), to describe how molecular diagnostics allows physicians to precisely identify the cause of a disease.[3] The term gained wider acceptance in 2011, when the US National Research Council published a report "Toward precision medicine", developing a framework for creating a new taxonomy of human disease based on molecular biology.[4] In 2015, the US

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president Barack Obama presented a notion of research with the main goal of accelerating progress towards a new era of PM.[5] Also in Europe, there are many initiatives promoting PM, for example, the "Precision Medicine for Cancer" conference organized by the European Association for Cancer Research and Organisation of European Cancer, a European Union parliament symposium on PM in allergy and airways,[1] or a position paper on applicability of PM in oncology now and in future published by the European Society for Medical Oncology.[6] The aim of this paper was to differentiate PM from personalized medicine, to show its potential benefits in the prevention, diagnosis, and treatment of chronic diseases, and to define problems with implementing it into clinical practice.

Precision medicine versus personalized medicine

Personalized medicine and PM are often used interchangeably because there is a considerable overlap between the two terms: both refer to "tailoring medical treatment to the individual characteristics of each patient"[4] and both have existed in scientific literature for many years. As of March 11, 2016, PubMed searches on "personalized medicine" and "precision medicine" yielded 27 451 hits and 18 690 hits, respectively. In both searches, the hit was a reference to an article titled "Technical problems in analysis of psychosomatic disorders with special reference to precision in short-term psychotherapy" by F. Dunbar, published in the *International Journal of Psychoanalysis* in 1952.[7] The aim of this paper was: "1) to call attention to the need for improving precision in short-term psychotherapy, 2) to suggest a means of selecting from among a large group of persons in need of treatment, for whom psychoanalysis is impossible or undesirable, those likely to respond best to briefer methods, 3) to point out that in determining the treatment of choice, the psychotic and somatic components in the illness syndrome must be evaluated not only quantitatively but also qualitatively, …".[7] It sounds modern despite the time it was written in.

The present meaning of "personalized medicine" entered the scientific lexicon in 1998 as a monograph title by Jain KK[8] and was recognized by scientists when they began to notice the potential of the Human Genome Project. The Personalized Medicine Coalition, founded in 2004, defined personalized medicine as "… the management of a patient's disease or disease predisposition, by using molecular analysis to achieve the optimal medical outcomes for that individual—thereby improving the quality of life and health, and potentially reducing overall healthcare costs".[9] Today they have modified their definition: "Personalized Medicine is an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from those tests with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans".[10]

There is some disagreement in the current definitions as to which questions, methods, and actions are part of personalized medicine.[11] Some definitions are narrow and refer only to the use of diagnostic test to predict drug response, others are wider and link personalized medicine with genetics, genomics, and other types of "omics", or show personalized medicine as a concept that has always existed, because "medicine always considered the needs of the individual".[11] The most appropriate definition that accommodates all these interpretations is "the use of combined knowledge about a person (genetics or otherwise) to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person's health".[11] It should be stressed that even this definition focuses on the individual patient and reinforces the idea of specific analyses for treatment of the individual.

One of the reasons for a change from "personalized medicine" towards a different term is the burden that comes with the phrase "personalized", sometimes misinterpreted as implying the idea of crafting a unique treatment for each individual.[4] Fully individualized therapy is difficult and demanding due to the complexity of the human body, heterogeneity of diseases, and high costs. Personalized medicine as an idea has not brought as many specific benefits from genomic analyses as enthusiasts of that notion were hoping. Precision medicine is more realistic and refers to the idea that molecular information will improve the accuracy with which patients can be classified and treated. The first objective is to better understand diseases and to refine a "New Taxonomy" that defines diseases based not only on symptoms and signs, but also on underlying molecular and environmental causes.[4] The main differences between personalized medicine and PM are: 1) PM focuses on patient subpopulations, which is an expansion of the individual focus of personalized medicine; 2) PM is a concept of integrating clinical and molecular data to better grasp and explain the biological basis of a disease in order to develop treatments with better outcomes for patients, whereas personalized medicine concentrates on individual aspects of a patient, based on which treatment is determined.[12] In this aspect, PM would help pave the way for a more patient-centered clinical practice described as "personalized medicine".

Precision medicine in the management of chronic disease

The benefits of PM have been shown clearly in relation to cancer.[6] Identification of HER2 as a prognostic biomarker in breast cancer has led to the development of a new drug, trastuzumab, an HER2-targeted monoclonal antibody used for treatment of HER2-positive breast cancer.[13] Tyrosine kinase inhibitors improved survival of patients with chronic myeloid leukemia (imatinib) and non-small-cell lung cancer (gefitinib and erlotinib). Due to genomic sequencing, genes notable in cancer biology have been identified.[14]

TABLE 1 Examples of chronic diseases in which precision medicine has been used

Branch of medicine	Disease	Biomarker	Intervention
pulmonology	cystic fibrosis	G551D	ivacaflor[16]
			ivacaflor/lumacaftor[17]
	asthma	IL-5	mepolizumab[18]
cardiology	coronary artery disease	CYP2C9	warfarin[19]
		CYP2C19	clopidogrel[20]
		SLCO1B1	statins[21]
metabolic disease	hypercholesterolemia	PCSK9	evolocumab, alirocumab[22]
hematology	thrombosis	factor V Leiden	avoid prothrombotic drugs[23]
nephrology	transplant rejection	urinary gene signature	antirejection drugs[24]
hepatology	hepatitis C	HCV NS5A	daclatasvir[25]
endocrinology	multiple endocrine neoplasia type 2	RET	prophylactic thyreoidectomy[26]
psychiatry	schizophrenia	CYP2D6	aripiprazole lauroxil,[27]
			brexpiprazole[28]
	alcohol-user disorder	GRIK1	topiramate[29]
neurology	autoimmune encephalitis	CXCL13	immunotherapy[30]
ophthalmology	Leber's congenital amaurosis	RPE65	gene therapy[31]

Lung cancer is an ideal example in which genome and transcriptome profiling have affected clinical outcomes.[15] Moving from histological classification to classification based on point mutations (BRAF V600E), copy number alterations (MET protooncogene, receptor tyrosine kinase amplification), and gene fusions (anaplastic lymphoma kinase [ALK] fusion), allowed to use targeted therapies.[15] Since the regulatory approval of imatinib to treat chronic myelogenous leukemia in 2001, approximately 50 targeted drugs have been developed and approved for treatment of many types of cancers.[14]

Oncology is not unique with the experiences of advancing and providing PM and has parallels in other areas of medicine. We have already witnessed successes of PM in the management of chronic disease.[16-31] Examples of targeted therapy and individual genetic profiling in order to avoid drugs that probably cause serious adverse effects listed in TABLE 1 are only the tip of the iceberg. One of the promises of PM is to accelerate our ability to recognize disease heterogeneity and to create new distinctions using large numbers of measurements on large populations of patients.

PM, an important modern paradigm for combining new types of metrics with large datasets, creates prediction models for prevention, diagnosis, and specific therapies in chronic diseases. The expanding use of wearable sensors for digital phenotypic assessment and behavioral monitoring provides a substantial amount of information and becomes part of everyday clinical practice, for example, in cardiology. Examples of PM strategies in chronic airway diseases, diabetes, and cardiovascular diseases are presented below.

Chronic airway diseases The PM strategy for chronic airway diseases is based on the presence of "treatable traits": airway smooth muscle contraction, loss of elastic recoil, and airway mucosal edema.[32] Reliable biomarkers for traits, for example, eosinophilic airway inflammation, could be used in the risk assessment and prediction of the response to treatment with corticosteroids.[32] Focus on biomarkers allows for a more effective and cost-effective treatment and development of more suitable drugs for airway diseases.

Diabetes Approaches of PM to diabetes should be reasonable and rational. Type 2 diabetes rarely affects each patient similarly and could be treated with more success if the patients were grouped into clinically varied subtypes with more precise prognoses. A recent study demonstrated that by adjusting diagnostic procedures and treatment to each patient, as well as by learning from an individual patient, PM shows great potential to improve health care.[33] A PM approach was used to characterize the diversity of type 2 diabetes patient populations based on high-dimensional electronic medical records (EMR) and genotype data from 11 210 individuals from Mount Sinai Medical Center in New York.[33]

First EMR data were clustered to identify type 2 diabetes patients from a greater group. Topological data analysis of the type 2 diabetes group established 3 new type 2 diabetes subtypes based on specific clinical characteristics and comorbidity of diseases. Type 2 diabetes complications including diabetic nephropathy and retinopathy characterized subtype 1; subtype 2 was burdened with cancer malignancy and cardiovascular diseases; and subtype 3 was associated most strongly with cardiovascular diseases, neurological diseases, allergies, and human immunodeficiency virus infections. Genetic association analysis identified 1279 single-nucleotide polymorphisms (SNPs)

that mapped to 425 unique genes specific to subtype 1, 1227 SNPs mapped to 322 unique genes specific to subtype 2, and 1338 SNPs that mapped to 437 unique genes specific to subtype 3. Based on these findings, type 2 diabetes would rather require tailored treatment plan instead of a one-size-fits-all approach. One of the goals of PM is to be able to determine the exact subtype sensitivity to therapies. Two important aspects of the study should be emphasized: 1) the possibility of utilizing the abundance of data that is gathered in the EMRs in order to reveal clinically significant patient population subgroups, and 2) revealing aspects considered high-priority for a follow-up study in type 2 diabetes patients based on the unique genetic component provided by this study.

Improving service delivery, policy development, research, and ultimately health outcomes is possible by developing a tool for monitoring disease risk. A post hoc analysis of the Diabetes Prevention Program delivers practical implications for the precise prevention of diabetes.[34] The study showed that: 1) multivariable model developed using Diabetes Prevention Program data and assessed risk factors could accurately predict progression to diabetes; 2) the probability of benefiting from diabetes prevention interventions substantially varies in high-risk diabetes patients; and 3) this benefit is different in individual patients, in whom prediabetes is a risk factor of early-onset diabetes.[34] In practice, by using an accurate risk prediction tool and through better risk targeting, a higher efficiency of lifestyle interventions and limited occurrence of the side effects of metformin could be achieved.

Cardiovascular diseases More than 50 years ago, the Framingham study introduced the concept of disease prediction based on patient-specific data or risk factors.[35] Polygenic models of risk are now tested along with traditional Framingham risk determinants in an effort to optimize the prediction of cardiovascular disease in routine clinical practice.[36] The genetic risk score comprising 13 SNPs associated with coronary heart disease is an independent predictor of cardiovascular events and of high coronary artery calcium. It provides a modest improvement in risk reclassification for coronary heart disease and a significant improvement in discrimination for high coronary artery calcium, a subclinical marker of coronary artery atherosclerosis, which in turn is an important risk factor for future cardiovascular events.[37]

Mining of clinical trial data enabled the development of many scoring systems, such as the CHA_2DS_2-VASc score, which allows greater efficiency in preventing thromboembolic stroke in atrial fibrillation due to individualized anticoagulation therapy.[38-41]

Cardiology is also a vanguard in applying some newer tools of the PM such as sophisticated phenotyping combined with machine learning to find patterns in robust, multifactorial data. One example is a study that demonstrated the feasibility and utility of phenomapping (high-density phenotyping classification) for the unbiased categorization of cardiovascular disorders.[42] Statistical learning algorithms applied to dense phenotypic data from multiple domains (67 continuous variables) allowed to cluster patients with heart failure with preserved ejection fraction into 3 separate groups that differed considerably in clinical characteristics, cardiac structure and function, invasive hemodynamics, and clinical outcome, indicating differing risk profiles and clinical trajectories (eg, phenogroup 3 had an increased risk of heart failure hospitalization).[42] In the future, phenomapping may lead to a better understanding of the phenotypic heterogeneity of heart failure with preserved ejection fraction, precisely redefining these conditions according to therapeutic responsiveness and to a more targeted treatment.

Integration of precision medicine into clinical practice Although precision medicine strategies have the potential for improving patient care, some major obstacles need to be conquered in order for this concept to be integrated into clinical practice. First of all, the health care infrastructure should provide necessary tools for clinicians and patients to enable data collection and processing and interpretation of results, as well as to facilitate treatment choices based on a new understanding of biological pathways. The broad expansion of EMRs, wearable devices, and health-focused mobile application software (so called mHealth, automated decision support software) creates the opportunity to redefine the way we manage chronic diseases (prevention, diagnosis, and treatment).

The key to bring PM into the mainstream is to introduce big data into the process of individually profiling diseases and patients. Big data is an ever-evolving term that describes any vast amount (petabytes and exabytes) of structured, semi-structured, and unstructured data with the potential to extract information. Big data can be characterized by volume (large data size), variety (various forms of data sources), velocity (high speed of change, high speed at which the data must be processed), veracity (uncertainty of data), and driving results (generating value).[12] Processing these voluminous and diverse data allows a development of new insights and discovery of new knowledge by incorporating data from manifold sources by clinical informatics within the health care informatics setting. The sources can be both internal and external to the EMRs, and countless rows and attributes can be used to the advantage of predictive modeling. Self-acquired data on lifestyle and environment collected from sensors and software could give researchers an insight into the factors that have so far been difficult to accurately assess.

The challenge for PM is to develop a network that links different "layers" of information relevant to health—from genetics and other

molecular characteristics to environmental exposures and social factors—and grounds it with individual patients who share their data. Determining the links between different types of data and the insights derived from them will help scientists understand diseases and develop more precise diagnostic, therapeutic, and preventive measures.[2] Advance in the science of medicine is associated with considering individuals as active partners, contrary to just patients or research subjects, which can be observed in change of medical practice and research culture.[2]

Challenges of big data analysis As the grounds of PM are built on big data, awareness of the unique concerns involved with big data application for precision medicine is important. One of the main concerns to providers of big data services is the issue of data storage. The 1000 genomes project data, for example, consists of more than 200 terabytes for the 1700 participants. Genomic data are not the only large datasets, which also include structured EMR data, unstructured clinical notes, medical imaging data, other data (epidemiological and behavioral), and drug databases. Analysts find PM particularly challenging. The big data problems, such as massive sample size, high heterogeneity, noise accumulation, spurious correlations, and incidental endogeneity, create the need for new statistical thinking and computational methods that are refined to data complexity, noises, and data dependence.[43] Finally, the issue of security of handling such big data needs to be raised.[44]

Conclusions The convergence of advancement in clinical informatics and inclusion of translational genomics is changing the way we approach the management of chronic diseases. Thanks to modern tools and technology, big data analyses allow both collection and to extraction of data concerning the groups of patients that show similar characteristics and require appropriate plans of prevention, diagnosis, and treatment. The extent to which these advances are constructive depends on our ability to implement new knowledge into clinical practice. Expectations must be realistic.

PM could call for a more proactive, rather than reactive, management of diseases and health care, including screening, early treatment, and prevention, and could revise the roles of both physicians and patients who become more involved in health care and health research. It would increase the reliance on EMRs and decision support systems. The complexity of data supporting PM will require health systems to provide diagnostics, informatics, and decision support to health care providers. On the other hand, handling such multiparametric data will require new educational models in medicine, with a greater focus on information management. To cope with this, regulatory bodies should establish frameworks that would ensure patient safety and would not hamper scientific progress.

The ability to better understand the diseases due to the progress in molecular biology will require a reclassification of diseases. The World Health Organization's International Classification of Diseases, which was established a century ago, must be modernized to include the constantly expanding molecular data on health and disease.

Potential long-term benefits of research in PM include: broader ability of physicians to use the "omics" information as part of routine clinical practice; better understanding of the mechanisms leading to numerous diseases; a revised approach to prevention, diagnosis, and treatment of a wide spectrum of diseases; a better integration of EMRs, data from sensors, software applications (mHealth), and numerous other sources in order to create an interactive network of knowledge that would improve the modeling and testing of both therapeutic and preventative strategies, empower further research, and inform the general public.

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ARTYKUŁ POGLĄDOWY

Medycyna precyzyjna w profilaktyce i leczeniu chorób przewlekłych

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SŁOWA KLUCZOWE

choroby przewlekłe, choroby układu krążenia, cukrzyca, medycyna precyzyjna, przewlekłe choroby układu oddechowego

STRESZCZENIE

Medycyna precyzyjna (*precision medicine* – PM) jest ważnym nowoczesnym sposobem połączenia nowych parametrów diagnostycznych i informacji uzyskanych z dużych baz danych medycznych w celu stworzenia modeli predykcyjnych dla profilaktyki, diagnostyki i specyficznej terapii w chorobach przewlekłych. Celem artykułu jest zwrócenie uwagi na różnice między PM a medycyną personalizowaną, wykazanie potencjalnych korzyści wynikających z zastosowania PM w leczeniu chorób przewlekłych oraz zdefiniowanie problemów związanych z wprowadzeniem PM do praktyki klinicznej. Przykłady zastosowania PM w przewlekłych chorobach układu oddechowego, cukrzycy i chorobach układu krążenia wskazują, że kluczową rolę w rozwoju PM ma wykorzystanie analizy dużych baz danych w procesie indywidualnej charakterystyki chorób i pacjentów. Wprowadzenie PM do praktyki klinicznej wymaga przebudowy infrastruktury opieki zdrowotnej poprzez włączenie niezbędnych lekarzom i pacjentom narzędzi umożliwiających gromadzenie i analizowanie danych, interpretowanie wyników i dokonywanie wyboru postępowania w oparciu o nowoczesną wiedzę dotyczącą szlaków biologicznych. Wielkość baz danych i ich duże zróżnicowanie stanowi znaczne wyzwanie techniczne i statystyczne. Potencjalne korzyści z zastosowania PM są następujące: 1) rozszerzenie możliwości zastosowania najnowszych osiągnięć genomiki, proteomiki, metabolomiki i innych dyscyplin wiedzy o nazwach zakończonych na „-omika" w rutynowej praktyce klinicznej, 2) lepsze zrozumienie patogenezy i epidemiologii chorób, 3) poprawa procesów zapobiegania, diagnostyki i leczenia chorób przewlekłych, 4) lepsza integracja elektronicznej dokumentacji medycznej oraz danych z czujników elektronicznych i aplikacji w interaktywnej sieci wiedzy służącej lepszemu planowaniu i sprawdzaniu strategii prewencyjnych i terapeutycznych, stymulowaniu dalszych badań i informowaniu społeczeństwa.

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