

## **Precision medicine/personalized medicine: a critical analysis of movements in the transformation of biomedicine in the early 21st century**

Medicina de precisão/medicina personalizada:  
análise crítica dos movimentos de transformação  
da biomedicina no início do século XXI

Medicina de precisión/medicina personalizada:  
análisis crítico de los movimientos de  
transformación de la biomedicina  
a inicios del siglo XXI

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### **Abstract**

*The enormous development of genomics research in recent decades has raised great expectations concerning its impact on biomedicine. There has been growing investment in research in personalized or precision medicine, which aims to customize medical practice with a focus on the individual, based on the use of genetic tests, identification of biomarkers, and development of targeted drugs. However, the personalized or precision medicine movement is controversial and has sparked an important debate between its defenders and critics. This essay aims to discuss the assumptions, promises, limits, and possibilities of personalized or precision medicine based on a review of the recent literature situating the debate on the theme. The review indicates that many of the promises of personalized or precision medicine remain unfulfilled. While there has been huge progress in knowledge on the molecular mechanisms of diseases and the development of drugs that have significantly impacted the treatment of some types of cancer, thus far there is no evidence that this same pattern will be reproduced in other complex diseases. Personalized or precision medicine is expected to generate incremental developments in specific areas of medicine, but there are obstacles to its generalization. The high cost of new biotechnologies can exacerbate health inequalities and become a problem for health services' sustainability, especially in low and middle-income countries. The emphasis on personalized or precision medicine may shift funds away from less costly interventions that have greater public health impact.*

*Precision Medicine; Personalized Medicine; Genomics; Innovation;  
Pharmaceutical Preparations*

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## Introduction

The enormous research investment and development in genomics and molecular biology in recent decades has raised great expectations concerning its impact on the transformation of medicine. Last-generation genome sequencing has significantly reduced its cost and increased its throughput, making this technology more accessible for research. This process and the post-genomics emphasis on new areas such as proteomics and metabolomics have contributed to the increase in the identification of biomarkers and the development of targeted drugs <sup>1</sup>.

Although the translation of genomic information and technology to clinical practice has not occurred at the pace initially anticipated by enthusiasts of genomics medicine, some authors contend that medicine is undergoing a process of “molecularization” <sup>2</sup> and that some areas, such as oncology, are being profoundly transformed by the incorporation of new knowledge and technologies.

A leading movement in the transformation of medicine is personalized or precision medicine, which aims to customize treatment according to the biological characteristics of individuals or subgroups in the population.

Based on identification of the patient’s genetic characteristics, personalized medicine promises to offer the precise drug at the exact dose and at the right time, making medical practice more efficient and decreasing healthcare costs <sup>3</sup>. Its defenders argue that the traditional “one-size-fits-all” medical approach to prevention, diagnosis, and treatment of diseases is inefficient, expensive, and sometimes dangerous due to adverse drug effects. Personalized medicine also assumes a transformation in the stance and subjectivity of patients, who are expected to become more proactive, contributing to the generation and interpretation of their own data <sup>3,4</sup>.

The last decade has witnessed a large and growing investment of capital in basic and applied research in personalized or precision medicine. In 2014, the United Kingdom launched the 100K Genomes Project with the objective of sequencing 100,000 genomes of patients in the National Health Service (NHS) in the search for biomarkers for cancer and rare genetic diseases. The project was unveiled by Prime Minister David Cameron and drew great media attention, having been proclaimed as an important step in the incorporation of genomics medicine into the heart of the NHS. In 2015, U.S. President Barack Obama announced to Congress the launching of a precision medicine program with a budget of 215 million dollars, to include genomic sequencing of 1 million persons, with the promise of becoming a milestone in the transformation of American medicine <sup>5</sup>. In 2016, China launched a 15-year program with 9.2 billion dollars in funding for precision medicine, aimed at making the country a global leader in the area <sup>6</sup>. There is clearly major investment in research in genomics and biotechnologies in health, with competition between developed and emerging countries for leadership in the production of this knowledge. This fact can be understood in a context of transition from industrial societies to information societies, in which knowledge has become the principal wealth of nations <sup>7</sup> and as biotechnologies (especially biomedical technology) have become the grand promise for the knowledge economy <sup>8</sup>.

In Brazil, genomic science and technology have been steadily incorporated by medical research, epidemiology (genome-wide association studies in genetic epidemiology), and clinical practice, especially in oncology. In 2015, with the support of the São Paulo State Research Foundation (FAPESP), the Brazilian Initiative on Precision Medicine (BIPMed) was launched in São Paulo, combining five research, innovation, and diffusion centers (CEPIDs) with the aim of creating the conditions for implementing precision medicine in Brazil <sup>9</sup>. Private laboratories in Brazil offer personalized medicine on their websites, proclaiming it as the medicine of the future. The available genetic tests feature genotyping of up to a million polymorphisms and complete exome sequencing, seeking to list the genetic mutations associated with diseases, to estimate genetic susceptibilities, and to produce information on personalized treatment with dozens of drugs.

However, the proposals and visions of the future in personalized medicine/precision medicine are not a consensus and have been the target of extensive criticism by researchers and clinicians concerned with their impact on research, medical practice, and health systems’ sustainability due to the new technologies’ high cost. An important debate is unfolding in the leading health journals, addressing the promises and impacts of personalized medicine/precision medicine, pitting its supporters against those who question the movement’s limits and the implicit risks for global health.

Many authors <sup>10,11,12,13</sup> question whether personalized medicine/precision medicine is really a route to a healthier world.

The social sciences play an important role in the analysis and discussion of these movements in the transformation of medicine, because science and medicine are social practices embedded in a historical, political, and sociocultural context. The incorporation of new technologies into medical practice is not due only to their clinical usefulness. Movements in the transformation of medicine are influenced by the political, historical, and socioeconomic contexts in which different stakeholders act: pharmaceutical and biotechnology industry, researchers, health professionals, politicians, patients' associations, citizens, media, and NGOs.

Personalized medicine/precision medicine's meanings have also changed in the last decade with the emergence of new terms (e.g., precision medicine) and the coexistence of groups that defend different directions for the movement, transcending its initial focus on pharmacogenomics and incorporating new biological, epigenetic, and socioenvironmental markers <sup>14</sup>.

Based on a critical socio-anthropological perspective, this essay aims to discuss the assumptions, promises, limits, and possibilities of personalized medicine/precision medicine and its possible impact on biomedicine, reviewing the recent literature that situates the current debate on the theme.

## Methods

A non-systematic review was performed of the last six years in the PubMed, Web of Science, and Google Scholar databases, using the descriptors “*personalized medicine*” and “*precision medicine*”. Given the existence of a vast literature on the theme, we selected the articles that focused on the current status, perspectives, expectations, or critiques of these movements in the transformation of medicine. The review incorporated pertinent articles found in the reviewed articles' reference lists. Thematic content analysis was performed to map the arguments for and against the proposal.

## The “technoscientization” of medicine and molecularization

In order to understand the personalized medicine/precision medicine movement, it is necessary to situate it in the context of the transformation of biomedicine in recent decades, towards what Clarke et al. <sup>15</sup> call technoscientific biomedicine. Anthropologists use the term “biomedicine” to refer to modern medicine due to its ontological and epistemological emphasis on biology. Biomedical discourse was built on the basis of scientific rationality and a biomechanistic conception of the body, grounded heavily in technologies for diagnosis and treatment of diseases. According to Clarke et al. <sup>15</sup>, since the mid-1980s, biomedicine has undergone a transformation in various dimensions, based on technoscientific innovations (computer and information technologies, molecular biology, biotechnologies, genomics, telemedicine/telehealth, etc.) that radicalize the process of technoscientization. The new technologies are causing institutional transformations with impacts on the production, distribution, and management of health information, diagnoses and treatments, and the very concept of what constitutes health and disease. This transformation at the political and economic level occurs in the integration between biomedicine and capitalist interests, in what authors call the “*Biomedical Technological Services Complex*”, referring to the increasingly industrialized medical-industrial and scientific complex, which move trillions of dollars around the globe.

The molecularization of biomedicine is part of this technoscientific transformation in which a new way of viewing and understanding the body at its molecular level complements or even supplants the traditional clinical view <sup>2</sup>. This process is characterized by a modification in the biomedical ways of thinking, assessing, and intervening, entailing a new conception of life as a set of vital mechanisms that can be identified, isolated, manipulated, mobilized, and recombined in new practices of intervention at the molecular level. Rose <sup>2</sup> emphasizes the idea that biology is no longer viewed as one's fate, but as an opportunity for technological intervention. Biology has become amenable to intervention and an area of major capital investment by the health industry.

Precision medicine is developing in a political and economic context of globalized capitalism, where one of the characteristics is what Rose calls “economies of vitality”. This is a new economic space, the bioeconomy, with a new form of capital, biocapital, in which the manipulation of life by biotech companies generates value.

Institutions such as the National Research Council of the National Academy of Science (USA) <sup>16</sup> and researchers like Kola & Bell <sup>17</sup> defend the need for a taxonomic change in the classification of diseases, based on their molecular characteristics. Based on the understanding of genomic and molecular variations in common diseases such as hypertension, the authors criticize the way diseases are still diagnosed as if they were homogeneous entities. The new taxonomy will no longer rest on the constellation of symptoms, the affected organ, or its anatomical characteristics, but on the disease’s molecular characteristics and pathways. Lung cancer, for example, is no longer viewed as a single disease, but as a set of rare diseases with different molecular characteristics. The diagnosis needs to be complemented by tumor genotyping, which detects genetic mutations such as the epidermal growth factor receptor (EGFR) mutation and the specific variant of this mutation (e.g., variant G719A), which allows choosing the best treatment.

### Meanings and assumptions of personalized medicine/precision medicine

Many researchers and clinicians use the terms “personalized medicine” and “precision medicine” as synonyms. In fact, more than differences between the two terms, one notes a certain fluidity in the way the concepts are defined and used. The term “personalized medicine” is older and was used quite widely in the last decade, but it has been replaced in recent years by “precision medicine”, lending the name to recent major research projects with genome sequencing in the United States and China. The term emerged in the late 1990s and was marked heavily by pharmacogenomics and the promise of developing adequate drugs for the genetic characteristics of population subgroups. However, its meaning has changed, with some authors <sup>3,18</sup> defending a more comprehensive approach, including not only individuals’ genetic and molecular information, but also other biomarkers and lifestyle, diet, and clinical data. This view is taken by the European Science Foundation <sup>3</sup> (p. 7), which defines personalized medicine as “*a new approach to classifying, understanding, treating, and preventing disease based on individual biological and environmental differences. It seeks to integrate data on the entire dynamic biological makeup of each individual as well as the environmental and lifestyle factors that interface with this makeup to generate a complex, individual phenotype*”.

Those who prefer the term “precision medicine” note that the concept of personalized medicine is not new, and that medicine has always been somewhat personalized in clinical practice <sup>19</sup>. They argue that the term may be misinterpreted, leading one to believe that it is the development of treatment and preventive measures specific to the individual, rather than population subgroups.

The term precision medicine was used for the first time in 2011 in a report by the U.S. National Academy of Sciences that proposed the basis for the elaboration of a new taxonomy of diseases based on molecular biology <sup>16,18</sup>. The report uses the term as a synonym for personalized medicine. The definition in the American project *Precision Medicine Initiative* is also quite similar to the way personalized medicine has been conceived: “*an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person*” <sup>20</sup>.

The similarity between the two terms has led some authors to ask whether the new denomination may not also represent a way of lending a fresh new start to the movement, leaving personalized medicine’s unfulfilled promises behind <sup>21</sup>. Given the similarity between the two terms and the fact that many researchers use them as synonyms, from here on we will refer to both simply as PM.

The central thrust of PM is the focus on the individual’s quantifiable data: genetic predispositions, lifestyle, diet, and clinical data to be incorporated into personal maps <sup>18</sup>. Importantly, these are not qualitative data that incorporate individuals’ narratives on their life and health/disease context, but structured, digitized, quantified, and computerized data <sup>18</sup>. Personalization is synonymous with intense characterization of the individual’s quantifiable data in different stages of health and disease over the course of life. PM thus proposes to lend meaning to a vast range of data, wagering on the development of computational technologies capable of simultaneously examining huge databases.

*“Precision medicine has emerged as a computational approach to functionally interpret omics and big data and facilitate their application to healthcare provision. In this new era, patients are not segregated by disease, or disease subtype. Instead, the aim is to treat every patient as an individual case, incorporating a range of personalized data including genomic, epigenetic, environmental, lifestyle, and medical history”* <sup>22</sup> (p. 494).

In this broader view, genomics is no longer the only actor on stage, but shares the scene with other actors, but without losing its leading role. The belief in genetic determinism was seriously shaken in the scientific community after the conclusion of the human genome mapping and dissemination of the results of genome-wide association studies, pointing to the low predictive power of genes. This broader view of PM was thus opened to greater complexity in its theoretical model with the inclusion of interaction between genes (at different molecular levels: proteomics, metabolomics, epigenetics, etc.) and environmental and lifestyle factors in the susceptibility to diseases.

The defenders of PM expect that computational algorithms will allow forming a virtual representation of the patient and developing predictive models based on known interactions between molecular, environmental, and lifestyle data, which in turn will allow individualized treatment decisions <sup>22</sup>. The expectation is that the future focus will shift from treatment of the disease to maintenance of the individual's health through personalized preventive medicine <sup>23</sup>.

Francis Collins, coordinator of the Human Genome Project, is a leading enthusiast of PM and of the new technologies' potential. Collins & Varmus <sup>5</sup> (p. 2) imagine a future in which: *“data from mobile devices might provide real-time monitoring of glucose, blood pressure, and cardiac rhythm; genotyping might reveal particular genetic variants that confer protection against specific diseases; fecal sampling might identify patterns of gut microbes that contribute to obesity; or blood tests might detect circulating tumor cells or tumor DNA that permit early detection of cancer or its recurrence”*.

New technologies such as artificial intelligence (deep learning/transfer learning) and blockchain (a decentralized system that structures data more securely) are emerging as promising approaches for dealing with enormous structured and unstructured databanks (big data) <sup>24</sup>, turning the expectations regarding PM into reality. These new technologies allow all the data on an individual to be transformed into medical data, such as facial images and videos, to become powerful data sources for predictive analysis <sup>24</sup>. Mamoshina et al. <sup>24</sup> defend a personal data-driven economy, arguing that patients should have complete knowledge and control over their medical data as a whole and should be able to manage them and be compensated for producing research data or for commercial purposes, besides incentives for monitoring health.

However, these visions of the future with constant monitoring of biomarkers still need to be problematized, since they represent a new level in the process of medicalization and the new forms of biopower. Clarke et al. <sup>15</sup> coined the term “biomedicalization” to refer to this process of intensification of medicalization based on the technoscientization of biomedicine. The characteristics of technoscientization are the commodification of health, turned into a consumer product, and biomedicalization, with the extension of medical jurisdiction beyond disease, encompassing health itself. The focus on health unfolds in the emphasis on practices in risk and susceptibility assessment and constant monitoring, aimed at staying healthy.

The PM discourse is part of this biomedicalization movement, placing the individual at the center of its epistemological and political perspective, in keeping with the dominant neoliberal philosophy. Individuals are urged to learn about their susceptibilities in order to monitor them, considerably increasing the amount of information they should consider when making decisions, as well as their responsibility in building a healthier future for themselves based on constant anticipatory orientation <sup>15,25</sup>. This emphasis on the individual also contributes to shifting the responsibility for healthcare from the social and political arenas to the individual level.

Metzler <sup>25</sup>, discussing the huge growth of studies aimed at identifying biomarkers for diseases, nevertheless questions the widespread conviction in the medical community that this is the proper route for medicine. She claims that the identification of biomarkers, one of the wagers by precision medicine to make clinical decision-making more robust, may actually increase its uncertainty and ambiguity. By transforming our understanding of what counts as health or disease and blurring the border between them, biomarkers may produce unwanted effects. Knowledge on biomarkers does not focus on the causes of diseases, but uses statistical methods to calculate susceptibilities, that is, the statistical association between a biological indicator and a health outcome. Some biomarkers provide

solid scientific evidence of the causative mechanisms of the disease, while others are only backed by the statistical power of big numbers, potentially generating false-positives with harmful consequences for the patient <sup>26</sup>. As Duffy <sup>22</sup> warns, more data do not necessarily mean more knowledge, and may also generate more noise. The dissemination of biomarkers in clinical practice may increase the creation of so-called “pre-symptomatic patients”, i.e., healthy persons medicalized due to their likelihood of becoming ill. The generation of a health database for each individual and the continuous monitoring of biomedical indicators may exacerbate in the population the notion that life is a process of waiting until a disease manifests itself <sup>22</sup>.

### Personalized medicine and its promises, breakthroughs, limits, and critiques

One of the points in the debate on PM relates to its promises and its effectiveness in delivering applications that bring relevant benefits in the health of individuals or populations. According to many critics, the promises have been overblown and excessively optimistic (so-called “hype”) <sup>10,11,12,19,27,28</sup>, given the large gap between the promises by researchers, pharmaceutical industry, and politicians in recent decades and the existing technical capacity to fulfill them.

Meanwhile, some authors <sup>29,30</sup> question the extent to which one can separate the expectations that will materialize from those that will fail (or the hype from the legitimate expectations), given the inherent uncertainty of any scientific undertaking. In the current context of biotechnologies, Rajan <sup>31</sup> created the term “venture science” to refer to a science that is promising, risky, and defined by a vision of the future that simultaneously mixes the production of scientific facts and capitalist value. In this context, the expectations play the role of mobilizing resources for the research, attracting the interest of the scientific community and financiers, with the justification of potential future clinical application <sup>32</sup>. Personalized medicine is at the center of this “promising economy of biotechnologies”, combining public benefit with the pursuit of commercial interests by the pharmaceutical industry and its investors <sup>29</sup>. The history of Theranos, a startup founded in 2003 that promised a revolution in the diagnostic tests market, is illustrative <sup>33</sup>. The company promised to perform dozens of tests for complex diseases with just a few drops of blood and succeeded in raising million dollars in investments to develop its innovative technology. As time went by, it became clear to investors that the promised technology would not live up to expectations, and the startup’s share value plummeted.

Many defenders of PM acknowledge that the expectation of a revolution in medicine, proclaimed during the Human Genome Project, has still not materialized, but they believe that it is only a matter of time <sup>3</sup>. They argue that it is unfair to demand immediate clinical application of PM, when history shows that it takes time for the results of basic research to reach the patient’s bedside <sup>22</sup>.

Other researchers such as Coote & Joyner <sup>10</sup> and Prasad <sup>11</sup> argue that the promises have not been delivered and that it is unlikely that they will be. Together with other authors <sup>12,19,28</sup>, they see the emphasis on precision medicine as an error that will not lead to the development of a healthier world. Others still defend the undertaking, but see a need to change the way it is being led <sup>34</sup>.

One of the reasons for the skepticism lies in the enormous complexity of the disease process in the more common noncommunicable diseases. Unlike monogenetic diseases, most of these diseases are caused by complex interaction between multiple genes with environmental factors, posing a major challenge for the realization of personalized medicine <sup>35,36</sup>. According to Duffy <sup>22</sup>, PM still has little to offer for treating complex multifactorial diseases, with the exception of the field of oncology.

Complete genomic sequencing became faster and less expensive with the introduction of new generation sequencing starting in 2005, when it became more accessible. Thus far, however, it has not proven highly useful in clinical practice, with the exception of rare genetic diseases, where it may come to be used earlier for diagnostic purposes, avoiding patients’ pilgrimage from one specialist to another and the need for various tests to reach a diagnosis <sup>37</sup>.

Gene therapy with genome editing has gained great impetus since the development of the CRISPR/Cas9 system (*Clustered Regularly Interspaced Short Palindromic Repeats*) in 2012. This tool has been described as revolutionary due to its low cost, speed, precision, and ease of use, with enormous potential for PM to offer a path to correct genetic mutations in rare and complex diseases <sup>38</sup>. CRISPR/Cas9 functions as a scissors that can identify and cut segments of DNA, pasting or replacing



pieces of the genetic code. The pharmaceutical industry is investing heavily in research on its use in clinical practice, but many technical obstacles still need to be overcome in order to achieve its full therapeutic potential<sup>38</sup>.

Regarding predictive tests, defenders of PM generally cite the genetic tests for the BRCA1 and 2 mutations, indicated to assess the risk of developing hereditary breast cancer and ovarian cancer, as a successful example of tests that can indicate lifetime risk of 85% for breast cancer and 65% for ovarian cancer. These tests can suggest preventive measures such as greater frequency of mammograms, prophylactic surgery, and chemotherapy, besides identifying other family members at risk. Although these tests had been available in clinical practice since the mid-1990s, they gained enormous visibility when Angelina Jolie announced in 2013 that she was a carrier of the BRCA1/2 gene mutations and had undergone a bilateral prophylactic mastectomy. The so-called “Angelina Jolie effect” greatly increased the demand for the BRCA1/2 tests by women from numerous countries, but it did not lead to a corresponding increase in the mastectomy rates<sup>39</sup>. Troiano et al.<sup>39</sup> discuss the enormous influence of celebrities and the media on patients’ behavior, but also raise questions on the need to promote precise, high-quality information for the population in order not to fuel a surplus of unnecessary tests for a low-risk population.

This concern is all the more relevant due to the widespread supply (in various countries) of genetic tests directly to consumers through companies like 23andMe, uBiome, or Miroculus. 23andMe offers genetic tests to inform people about their ancestry and genetic susceptibilities, measuring risks for a series of conditions, such as: macular degeneration, hereditary thrombophilia, Parkinson’s disease, Alzheimer’s disease, and hereditary hemochromatosis, among others. The consumer orders the sample collection kit over the internet, collects the sample at home, and sends it to the company by mail, receiving the results several weeks later. In 2018, 23andMe announced the approval by the FDA (Food and Drug Administration) for marketing the BRCA1/2 genetic tests directly to consumers, without the need for a medical prescription or genetic counseling. The announcement raised apprehension among researchers and physicians, who alerted the public to the fact that many women may have a false sense of security if they fail to understand that the commercial test is limited largely to identifying the genetic variants found in Ashkenazi Jewish women and rare in the overall population<sup>40</sup>.

Despite enthusiasm by the companies marketing genetic tests, the promise of estimating genetic susceptibility based on polymorphisms for complex diseases such as cancer, diabetes, cardiorespiratory diseases, schizophrenia, or depression has still not materialized. Genome-wide association studies have pointed to modest genetic associations with a slight increase in the risk of disease and with little predictive value when compared to the more significant contributions of environmental risks, family history, or social and behavioral factors<sup>35,37</sup>. According to Tutton<sup>19</sup>, the companies marketing genetic susceptibility tests are undertaking a reinterpretation of genome-wide association studies (GWAS), using the results of statistical associations between genetic variants and health outcomes in populations as if they were predictive of individual risks.

Another questionable assumption is that PM will contribute to persons’ adoption of preventive measures based on knowledge of their genetic susceptibilities. Several studies have problematized this claim and shown that genetic information with personalized orientation does not necessarily lead to behavior change by the persons at risk<sup>12,22,35</sup>. The low impact of actions targeted to high-risk individuals is a point frequently overlooked by defenders of PM<sup>12</sup>.

Oncology is the medical field that is most incorporating the new genomic technologies in the identification of tumors’ molecular profile and use of targeted drugs, including immune therapy, frequently cited by PM as a success story. Treatments with targeted drugs, which act on genetic mutations, have generated significant improvement in clinical results for some types of cancer. For breast cancer, trastuzumab associated with the genetic test for tumors that express the HER2 protein and imatinib in the treatment of chronic myeloid leukemia (CML) have completely transformed the treatment paradigm for these diseases, providing significant clinical improvement for patients<sup>41</sup>. In the treatment of colorectal cancer, for example, patients that receive cetuximab and chemotherapy show a better therapeutic response than those on chemotherapy alone. Only patients with a genetic variation (mutant KRAS) fail to benefit from the drug<sup>35</sup>.

Gene panels are being used in breast cancer to identify women who can be spared of more aggressive treatments like chemotherapy. The year 2018 witnessed major media attention for the TAILORx

study, whose genetic test, called Oncotype DX Breast Cancer Assay, based on the analysis of 21 tumor genes, managed to safely identify women with early-stage breast cancer who could receive only hormone therapy, avoiding chemotherapy. An estimated 70% of patients with early-stage breast cancer could avoid chemotherapy <sup>42</sup>.

Immune therapy is seen as the most recent and promising cancer treatment technology for stimulation of the patient's immune system to recognize and eliminate the tumor. Antibodies acting on negative immune response regulators such as CTLA-4 and PD-1 showed significant improvement in long-term survival, especially in melanoma <sup>36</sup>. The first drugs, such as ipilimumab, started reaching the market in 2011, followed by more effective second-generation drugs like nivolumab and pembrolizumab.

However, this progress is only one side of the coin. In a recent review article, Sell <sup>43</sup> calls attention to the fact that the history of immune therapy in cancer has been marked by high levels of enthusiasm following anecdotal case reports with huge therapeutic success, followed by waning levels of enthusiasm when the results of controlled clinical trials become available, showing that the gains are incremental and limited to a relatively small number of patients with a specific type of cancer <sup>43</sup>.

Regarding targeted drugs, the problem identified by Maughan <sup>36</sup> is that the expectation of a paradigm shift inspired by drugs like imatinib and trastuzumab did not become a reality, and they are the only ones among the few examples of targeted therapy that provide significant long-term improvement with single agents. Most of the new targeted drugs fail to achieve the same benefits. Fojo et al. <sup>44</sup> showed that the mean improvement in overall survival with 71 new drugs approved by the FDA for cancer treatment from 2002 and 2014 was only 2.1 months.

The main difficulty is the resistance to targeted drugs used against cancer because of tumor heterogeneity and the clonal evolution that exists in many cancers <sup>10,27,36,45</sup>. Targeted drugs, based on the analysis of tumor mutations, only eliminate the susceptible clones, leaving the resistant and adapted cells alive, causing resistance to the drug <sup>10,42</sup>. Targeted therapies such as BRAF(V600) inhibitors in malignant melanoma may lead to major clinical improvement, but it is frequently short-lived, to the extent that the tumors adapt rapidly and produce resistance to the drug <sup>22,45</sup>.

According to Maughan <sup>36</sup>, the beneficial and lasting effects of imatinib in the case of CML are the exception rather than the rule, since this disease is caused by a very specific and unique genetic alteration. Most cancers are caused by a mix of genetic abnormalities that vary according to the site and between individuals, and which are heavily influenced by environmental factors <sup>36</sup>. Maughan, although acknowledging the strides in knowledge on the molecular mechanisms of diseases and some therapeutic applications, criticizes the way the extraordinary results of a few technologies are repeated in the conferences on PM and achieve mythical proportions, without the counterpoint of the limits and failures to reproduce these benefits in more complex diseases. In the same sense, Prasad <sup>11</sup> points out that a very small number of patients benefit from precision oncology and states that it is still a "hypothesis that needs verification".

Based on today's available evidence, a moderate tone in relation to the promises of PM is prudent. PM may not represent the revolution in medical care that it promises, but it may bring mainly an incremental gain on a case-by-case basis <sup>22</sup> and in certain niches <sup>10</sup>, as observed in certain types of cancer. Neither can the penetration of genomic technology in medicine be generalized, since there are many areas in which such technologies have not penetrated, and even in oncology there are types of cancers in which genomic technology has not led to progress. Some authors thus question the robustness of the molecularization process, asking whether it is really a revolution (with the replacement of traditional medical practices) or an evolution with complementary coexistence of these practices <sup>1</sup>.

### **The high cost of targeted drugs and the inequalities in access to the benefits**

One of the great promises of precision medicine is to reduce the cost of medical care, based on greater efficiency in the use of drugs, avoiding their use in patients in which they would be ineffective or avoiding side effects. However, this promise has not materialized. To the contrary, the high cost of targeted drugs produces inequalities in access to the drugs' benefits and challenges for health systems' sustainability <sup>41,46</sup>. The cost of new cancer drugs has grown rapidly and continuously <sup>44</sup>, and their



average cost per patient often exceeds a USD 100,000 a year<sup>47</sup>. Factors contributing to the rising costs include the fact that the drugs frequently need to be combined to reach the best clinical results, as in the case of the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA4), the cost of which reaches USD 252,000 a year<sup>47</sup>. Another important factor is that the drug prices have not fallen over time as expected, despite the availability of generic drugs. Imatinib, for example, has quadrupled its prices in the United States since it was launched<sup>48</sup>.

One of the main factors in the rising costs of cancer treatment is the growing use of high-cost new drugs for approved indications and also for unproven (“off label”) indications, and which bring modest benefits for patients<sup>44</sup>. Fojo et al.<sup>44</sup> criticize the low requirement of the criteria used by the ASCO (American Society of Clinical Oncology) committee to assess whether a drug provides clinically significant improvement (improved survival and/or quality of life). According to the latter authors, the low threshold of requirement for efficacy is resulting in stimulus for manufacturing redundant drugs (the “me too” mentality), which bring treatment options for patients, but with modest benefits in relation to their high cost. Of the 71 new drugs approved by the FDA from 2002 to 2014, only 30 (42%) could be considered as providing significant clinical improvement (in survival or quality of life), despite the low requirements for benefits<sup>44</sup>. The authors point out that the “me too mentality” is an important factor for the industry not to run risks by investing in studies that might result in significant innovation.

Various authors believe that this tendency to produce high-cost drugs for modest benefit in small groups cannot be sustained for long<sup>29,47</sup>. Ferreira et al.<sup>46</sup> acknowledge the benefits of targeted drugs, but point out that the real value of new interventions in comparison with established strategies has still not been properly assessed in comparative studies. A systematic assessment of the drugs approved by the EMA (European Medicines Agency) from 2009 to 2013 showed that many drugs for cancer treatment entered the market without evidence of benefit in terms of survival or quality of life<sup>49</sup>.

For Sturdy<sup>29</sup>, personalized medicine has been better at keeping its promise to compensate private investment in the pharmaceutical and biotechnology industry than in providing savings for health services. According to the author, this logic means that research and technologies that could lead to cost reductions for health services (but would jeopardize corporate profitability) end up losing out to the production of high-cost drugs<sup>29</sup>.

The price of new drugs, especially in the United States, is based only on market acceptability, overlooking the innovation’s cost or the benefit they provide<sup>41</sup>. Any new cancer drug is presented as having a high intrinsic moral value regardless of its cost to society. High prices have become a norm with a global impact, given the importance of the American market as the parameter for price-setting elsewhere in the world<sup>41</sup>.

The high cost of targeted drugs will entail inequalities in access to the benefits between high and middle/low-income countries and within these countries, between populations from different social strata. For low-income countries that often experience difficulties in accessing basic health technologies for their populations, the costs of the new treatments are prohibitive. Most low and middle-income countries are unable to provide their populations with all the drugs that are considered essential by the World Health Organization (WHO)<sup>41</sup>. Thus, PM may concentrate resources in the part of the population that already has higher purchasing power and better access to health services.

### Shifting research priorities

Finally, one of the problems detected by critics of PM is the degree to which the emphasis by governments, funding agencies, the pharmaceutical industry, and the scientific community on genomic and molecular health research is changing the research priorities and relegating to a lesser level the attention to social determinants of health and preventive measures with greater impact for the population<sup>13,19,35,36,50</sup>. Bayer & Galea<sup>13</sup> show that funding from the NIH (National Institutes of Health) in 2014 for research areas that included the words “gene, genome, or genetic” was 50% greater than for areas that included the word “prevention”. According to Khoury & Galea<sup>35</sup>, NIH funding for research in public health has declined in the last ten years, while funding for genomics research has grown substantially. We agree with Joyner & Paneth<sup>28</sup> on the importance of problematizing the impact, in public

health terms, of the enormous investment in PM. What are the contributions by PM in dealing with the major global public health problems? Will PM reduce the main causes of morbidity and mortality?

Our accumulated knowledge on the social determinants of health shows that the main public health problems will not be affected by personalized medicines if the principal underlying social causes of these problems are not effectively addressed. The great strides in the improvement of population health indicators resulted from improvement in the population's socioeconomic conditions and key measures for population groups such as basic sanitation, vaccination, and tobacco control programs<sup>28</sup>. The priority approach in PM, with emphasis on high-cost drugs to benefit small populations, not only will fail to produce greater population impact, but may also override low-cost and more effective population interventions and policies<sup>10,22</sup>. According to Maughan<sup>36</sup>, in order to make progress in reducing cancer mortality, the focus should be on primary prevention, early detection, and optimization of treatment immediately after diagnosis.

The overblown optimism with the promises of PM and its focus on the individual also have an impact on the clinical encounter. Maughan<sup>36</sup> cites the case of patients who already come to the physician's office asking for a prescription of the new drug they have researched on the internet. According to researchers and physicians, PM may contribute to the emergence of a new generation that views the world through individualist lenses<sup>35</sup>.

## Conclusion

The PM movement is highly controversial and has sparked heated debates. The promises raise great expectations concerning the potential of the new genomic and molecular technologies for the prevention and treatment of complex diseases. However, evidence suggests that caution and more restraint are necessary in relation to personalized medicine's promises. While there has been huge progress in knowledge on the molecular mechanisms of diseases and the development of drugs with an enormous impact on the treatment of some types of cancer, these successes cannot be interpreted as paradigm shifts, since there is still no evidence that this pattern will be reproduced in other complex diseases.

The central focus on the individual and on high-cost technologies that benefit a small portion of the population not only will fail to reduce the main health problems affecting the world, but may also increase the inequalities, with concentration of resources and technologies in the population strata that already have the best access to health, thereby exacerbating health inequalities and hampering health services' sustainability, especially in low and middle-income countries. For the incorporation of new technologies in personalized medicine, it is essential to undertake a cost-benefit assessment from an ethical perspective that considers whether they will be accessible for everyone to benefit and will not exacerbate the existing health disparities.

The emphasis on individuals and genomic knowledge needs to be counterbalanced with the subjects' understanding in their sociocultural, political, and economic contexts and with the equivalent investment in actions on the social determinants of health. The social sciences perspective shows us that biomedical technologies are not neutral. They have a history, they are part of a moral context, and their clinical application is heavily influenced by cultural norms, political and economic interests, and dominant scientific trends<sup>51</sup>. A critical analysis is thus essential on the assumptions, practices, and possible consequence of PM. The social sciences can contribute to this undertaking, situating the subject and the biological body in their historical, political, environmental, and economic contexts, addressing the repercussions of the implementation of new genomic technologies on clinical practice, based on local knowledge and the experience of health professionals, patients, and communities directly affected by the technological innovations<sup>51,52</sup>.

## Additional information

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## Resumo

O grande desenvolvimento da pesquisa em genômica nas últimas décadas tem gerado muitas expectativas com relação ao seu impacto na biomedicina. Observa-se o crescente investimento em pesquisa na medicina personalizada ou de precisão, que busca customizar a prática médica com foco no indivíduo baseando-se na utilização de testes genéticos, identificação de biomarcadores e desenvolvimento de medicações alvo. O movimento da medicina personalizada ou de precisão, no entanto, é polêmico e tem suscitado um importante debate entre seus defensores e críticos. Este ensaio teve por objetivo discutir os pressupostos, promessas, limites e possibilidades da medicina personalizada ou de precisão com base em uma revisão da literatura recente situando o debate sobre o tema. A revisão aponta que muitas das promessas da medicina personalizada ou de precisão ainda não se concretizaram. Se por um lado houve enorme avanço no conhecimento sobre os mecanismos moleculares das patologias e o desenvolvimento de medicamentos que impactaram significativamente o tratamento de alguns tipos de câncer, até o momento não há evidências de que este padrão se reproduzirá em outras doenças complexas. A medicina personalizada ou de precisão deve gerar desenvolvimentos incrementais em áreas específicas da medicina, existindo, no entanto, vários obstáculos para sua generalização. O alto custo das novas biotecnologias pode agravar as desigualdades em saúde, tornando-se um problema para a sustentabilidade dos serviços de saúde, especialmente em países de média e baixa rendas. A ênfase na medicina personalizada ou de precisão pode levar ao deslocamento de recursos financeiros de iniciativas menos custosas e com maior impacto em saúde pública.

*Medicina de Precisão; Medicina Personalizada; Genômica; Inovação; Preparações Farmacêuticas*

## Resumen

El gran desarrollo de la investigación en genómica en las últimas décadas ha generado muchas expectativas en relación con su impacto en la biomedicina. Se observa la creciente inversión en investigación en medicina personalizada o de precisión, que busca hacer a medida la práctica médica, centrándose en el individuo, basándose en la utilización de pruebas genéticas, identificación de biomarcadores y desarrollo de medicamentos diana. El movimiento de la medicina personalizada o de precisión, no obstante, es polémico y ha suscitado un importante debate entre sus defensores y críticos. Este ensayo tuvo como objetivo discutir los presupuestos, promesas, límites y posibilidades de la medicina personalizada o de precisión, en base a una revisión de la literatura reciente, situando el debate sobre este tema. La revisión apunta que muchas de las promesas de la medicina personalizada o de precisión todavía no se concretizaron. Si por un lado hubo un enorme avance en el conocimiento sobre los mecanismos moleculares de las patologías, y el desarrollo de medicamentos que impactaron significativamente el tratamiento de algunos tipos de cáncer, hasta el momento no hay evidencias de que este patrón se reproducirá en otras enfermedades complejas. La medicina personalizada o de precisión debe generar desarrollos incrementales en áreas específicas de la medicina, existiendo, no obstante, varios obstáculos para su generalización. El alto coste de las nuevas biotecnologías puede agravar las desigualdades en salud, convirtiéndose en un problema para la sostenibilidad de los servicios de salud, especialmente en países de media y baja renta. El énfasis en la medicina personalizada o de precisión puede llevar al desplazamiento de recursos financieros de iniciativas menos costosas y con mayor impacto en salud pública a otras de esta índole.

*Medicina de Precisión; Medicina Personalizada; Genômica; Innovación; Preparaciones Farmacéuticas*

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