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Personalized medicine: overview and comparison of challenges and opportunities for its implementation in the Brazilian public healthcare system (SUS)

Medicina personalizada: panorama e comparação de desafios e oportunidades para sua implantação no SUS

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ABSTRACT

The objective of this work is, through a literature review, to promote the debate on personalized medicine and acquire a broad view of the subject and its tools from the perspective of oncology, disseminate the topic, support, and encourage initiatives to implement its technologies in the Brazilian public healthcare system, collaborating for a sustainable ecosystem in the incorporation of technologies, and above all, with the health and quality of life of patients. The implementation of personalized medicine technologies in SUS is feasible and effective. The scenario is optimistic considering the latest updates from the Ministry of Health with the establishment of the Brazilian Genomes Program. With wise management of resources and actions focused on creating an infrastructure that supports it, the entire public healthcare system will be benefited and can take advantage of the improvements. Personalized medicine is the future of healthcare.

Keywords: Precision medicine; Healthcare financing; Healthcare disparities; Health care economics and organizations.

RESUMO

O objetivo deste trabalho é, por meio de uma revisão de literatura, promover o debate sobre a medicina personalizada e adquirir uma visão ampla sobre o assunto e suas ferramentas sob a ótica da oncologia, divulgar o tema, apoiar e incentivar iniciativas de implementação de suas tecnologias no sistema público de saúde brasileiro, colaborando para um ecossistema sustentável na incorporação de tecnologias e, sobretudo, com a saúde e qualidade de vida dos pacientes. A implementação de tecnologias de Medicina Personalizada no SUS é viável e eficaz. O cenário é otimista considerando as últimas atualizações do Ministério da Saúde com a instituição do Programa Genomas Brasil. Com uma gestão criteriosa dos recursos e ações voltadas para a criação de uma infraestrutura que a sustente, todo o sistema público de saúde será beneficiado e poderá usufruir das melhorias. A medicina personalizada é o futuro dos cuidados de saúde.

Descritores: Medicina de precisão; Financiamento da saúde; Disparidades de saúde; Economia e organizações de cuidados de saúde.

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INTRODUCTION

Personalized medicine

The term personalized medicine was first used in 1999 by Robert Langreth and Michael Waldholz,[3] and currently also known as precision medicine or individualized medicine, it brings the interpretation of looking at the patient as unique in their journey and can be popularly defined as "to provide the right diagnosis and treatment for the right patient at the right time". The essence of this principle permeates the fact that each patient is unique and must receive medications appropriate to their specific clinical needs to optimize treatment and minimize possible harm.[1]

Jørgensen (2019)[1] discusses in his article for "The Oncologist" in 2019 the various definitions f or what is personalized medicine but concludes that even 20 years after the first mention, there is still no consensus.[1] The definitions from the National Cancer Institute (NCI), the Food and Drug Administration (FDA), and the Council of the European Union are listed in Table 1 below.

In addition to the definitions presented in Table 1, the Council of the European Union also states that personalized medicine is broadly correlated with a greater concept of central patient care, which considers that the healthcare system must respond to their needs.[1]

Also in the same article, Jørgensen (2019)[1] discusses the differences between the terms personalized medicine and precision medicine. From the definitions presented by the NCI and FDA, he concludes that institutions do not distinguish between the two terms and are therefore interchangeable, or at least very similar.[1] The European Society of Medical Oncology (ESMO) has discussed the use of the two terms and considers them interchangeable.[2] Thus, we consider the terms interchangeable in this work.

In the analysis of the use of the terms personalized medicine, precision medicine, and stratified medicine, Jørgensen (2019)[1] found that between 2003 and the end of 2008 the number of publications using the term personalized medicine was higher than the other terms. However, as of 2009, the term precision medicine became more popular and currently surpassed the number of publications with the term personalized medicine. The term stratified medicine, on the other hand, seems to have gained strength from 2013, but it was not highlighted compared to the other terms, as can be seen in the Graph 1.[1]

In an article published by "The Oncologist" in 1999, the authors stated that in the pharmacotherapeutic approach of one-size-fits-all (a term that is now used in the pharmaceutical market as a synonym for outdated), the best drugs work in only 50% a 70% of patients. In this article, the idea that knowledge about genetic variability could improve treatment outcomes for each patient was also presented.[3]

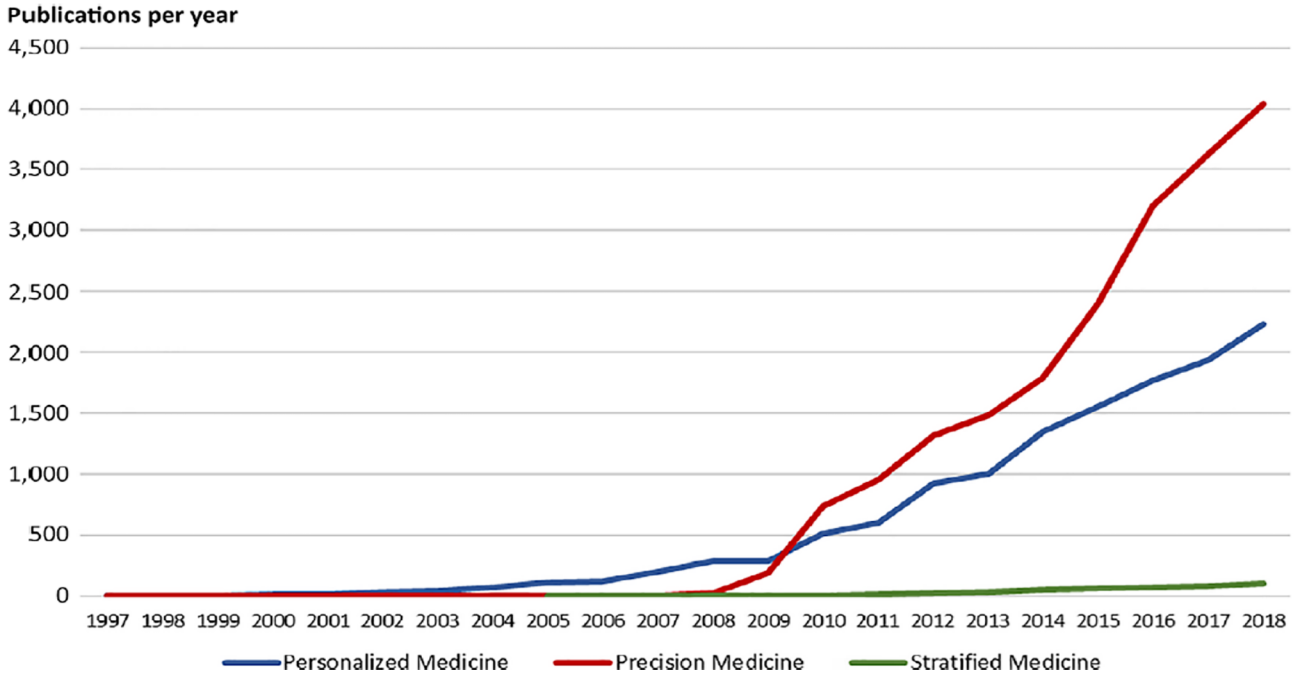
Thus, from the need for increasingly effective treatments and with the advent of genomic technologies, it is very clear that the development and implementation of personalized medicine go hand in hand with the development of relevant diagnostic methodologies.[1]

It is understood that the prediction of biomarkers is one of the most important elements for carrying out personalized medicine, if not the most important. Biomarker research is used to identify patients who would be more likely to have a positive response to a given pharmacotherapy, enabling treatment individualization, and avoiding expensive and inappropriate treatments. Thus, the regulatory terms for these biomarker prediction tests are companion diagnostics or complementary diagnostics.[1]

With the increasing role of companion diagnosis in drug development and clinical practice, some countries such as Australia, Canada, the European Union, Japan, and the United States have adopted guidelines and legislation on the subject in recent years. By 2019, in the United States, more than 30 different types of drugs were approved in combination with their complementary diagnostic methods.[1]

Table 1. Definitions of personalized medicine from the main institutions mentioned by Jørgensen (2019).[1]

Institution	Definition
NCI	A form of medicine that uses information about genes, proteins, and the environment to prevent, diagnose, and treat diseases. In cancer, personalized medicine uses information about a person's tumor to help diagnose, plan treatment, find out if the treatment is working well, or make a prognosis. Examples of personalized medicine include using targeted therapies to treat specific types of cancer cells, such as HER2-positive breast cancer cells, or using tumor marker testing to help diagnose cancer. Also called precision medicine.[1]
FDA	Precision medicine sometimes known as 'personalized medicine' is an innovative approach to adapting disease prevention and treatment that considers differences in people's genes, environments, and lifestyles. The goal of precision medicine is to get the right treatments to the right patients at the right time.[1]
Council of the European Union	Personalized medicine refers to a medical model that uses the characterization of phenotypes and genotypes of individuals (e.g., molecular profile, medical images, lifestyle data) to adapt the right therapeutic strategy to the right person at the right time, and/or to determine predisposition to disease and/or to provide timely and targeted prevention.[1]



Graph 1. The number of publications per year containing each term. Graph-based on PubMED searches using the terms mentioned. Updated in January 2019.[1]

The concept of companion diagnostics had already been described in the same 1999 article, but still without using this terminology. The authors discussed the idea that a simple diagnostic test could provide precious information on which patients could benefit from a given treatment and which could present risks of developing adverse events.[3] Trastuzumab was the first drug developed using the drug-diagnostic co-development model in 1998, one year before the publication that introduced the term personalized medicine. It was in that year that the FDA simultaneously approved trastuzumab (Herceptin; Genentech, South San Francisco, CA) - for the treatment of patients with metastatic breast cancer whose tumor overexpresses the human epidermal growth factor receptor-type 2 (HER2) protein - and immunohistochemical evaluation (HercepTest; Dako, Glostrup, Denmark) to detect HER2 overexpression in tumor tissue. Since then, the co-development of drug-diagnostics has proven to be a successful model over the years, especially in oncology and hematology.[1]

Chart 1, below, shows the drugs approved by the FDA, until 2019, with companion diagnostics methods linked to their use:

Chart 1. Drugs approved by the FDA, until 2019, with companion diagnostics methods linked to their use.[1]

Drug	Indication	Companion diagnostic
Ado-trastuzumab Emtansine	Breast cancer	HercepTest
		Dako HER2 FISH PharmDx Kit
Afatinib	Non-small cell lung cancer	Therascreen EGFR RGQ PCR Kit
		FoundationOne CDx (F1CDx)
Alectinib	Non-small cell lung cancer	FoundationOne CDx (FICDx)
		Ventana ALK (D5F3) CDx Assay
Atezolizumab	Urothelial carcinoma	Ventana PD-L1 (SP142) Assay
	Non-small cell lung cancer	Ventana PD-L1 (SP142) Assay
Binimetinib	Melanoma	THxID BRAF Kit
Brigatinib	Non-small cell lung cancer	Vysis ALK Break Apart FISH Probe Kit
Ceritinib	Non-small cell lung cancer	Vysis ALK Break Apart FISH Probe Kit
		Ventana ALK (D5F3) CDx Assay
Cetuximab	Colorectal cancer	Cobas KRAS Mutation Test
		Dako EGFR PharmDx Kit

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Drug	Indication	Companion diagnostic
Crizotinib	Non-small cell lung cancer	Oncomine Dx Target Test
		Vysis ALK Break Apart FISH Probe Kit
		Ventana ALK (D5F3) CDx Assay
Cobimetinib	Melanoma	Cobas 4800 BRAF V600 Mutation Test
Dabrafenib	Melanoma	THxID BRAF Kit
	Non-small cell lung cancer	Oncomine Dx Target Test
Dacomitinib	Non-small cell lung cancer	Therascreen EGFR RGQ PCR Kit
Deferasirox	Thalassemia	Ferriscan
Enasidenib	Acute myeloid leukemia	Abbott RealTime IDH2
Encorafenib	Melanoma	THxID BRAF Kit
Erlotinib	Non-small cell lung cancer	Cobas EGFR Mutation Test v2
		FoundationOne CDx (FICDx)
Gefitinib	Non-small cell lung cancer	Oncomine Dx Target Test
		Therascreen EGFR RGQ PCR Kit
		Cobas EGFR Mutation Test v2
Gilteritinib	Acute myeloid leukemia	LeukoStrat CDx FLT3 Mutation Assay
Imatinib Mesylate	Aggressive systemic mastocytosis	KIT D816V Assay
	Gastro intestinal stromal tumor	Dako C-KIT PharmDx
	Myelodysplastic syndrome	PDGFRB FISH Assay
Ivosidenib	Acute myeloid leukemia	Abbott RealTime IDH1
Lorlatinib	Non-small cell lung cancer	Vysis ALK Break Apart FISH Probe Kit
Midostaurin	Acute myeloid leukemia	LeukoStrat CDx FLT3 Mutation Assay
Nilotinib	Chronic myeloid leukemia	MolecularMD MRDx BCR-ABL Test
Olaparib	Ovarian cancer	BRACAnalysis CDx
	Breast cancer	BRACAnalysis CDx
Osimertinib	Non-small cell lung cancer	Cobas EGFR Mutation Test v2
		FoundationOne CDx (FICDx)
Panitumumab	Colorectal cancer	Praxis Extended RAS Panei
		Therascreen KRAS RGQ PCR Kit
Pembrolizumab	Non-small cell lung cancer	Dako PD-L1 IHC 22C3 pharmDx
	Gastroesophageal adenocarcinoma	Dako PD-L1 IHC 22C3 pharmDx
	Cervical cancer	Dako PD-L1 IHC 22C3 pharmDx
	Urothelial carcinoma	Dako PD-L1 IHC 22C3 pharmDx
Pertuzumab	Breast cancer	HercepTest
		HER2 FISH PharmDx Kit
		FoundationOne CDx (FICDx)
Rucaparib	Ovarian cancer	FoundationFocus CDxBRCA Assay
Talazoparib	Breast cancer	BRACAnalysis CDx
Trametinib	Melanoma	THxID BRAF Kit
	Non-small cell lung cancer	Oncomine Dx Target Test
Trastuzumab	Breast cancer	HercepTest
		Pathway ANTI-HER-2/NEU (4B5)
	Gastric cancer	HercepTest
		Dako HER2 FISH PharmDx Kit
Vemurafenib	Melanoma	Cobas 4800 BRAF V600 Mutation Test
		FoundationOne CDx (FICDx)
Venetoclax	Chronic lymphocytic leukemia	Vysis CLL FISH Probe Kit

The recent approval of larotrectinib (Vitrakvi; Loxo Oncology/Bayer) for patients with neurotrophic tyrosine receptor kinase (NTREK) gene fusion and pembrolizumab (Keytruda; Merck Sharp & Dohme, Chalfont, PA) for patients with high microsatellite instability (MSI-H) and positive incompatibility repair deficiency (dMMR) marks the breaking of a paradigm in the development of drugs targeted to biomarkers. Compared to the drugs that were being developed so far since trastuzumab, larotrectinib and pembrolizumab were not developed for a conventional cancer indication defined by histology and tumor origin, but only in their effect related to specific molecular characteristics. So, we have a new trend incorporated into the concept of personalized medicine.[1]

Jørgensen (2019)[1] further concludes that personalized medicine should be considered as an ongoing effort to individualize pharmacotherapy. With advances in molecular medicine, our ability to interpret the pathophysiology and mechanisms of action of drugs has increased. Drugs act at the molecular level, and thus, finding more effective solutions to individualize pharmacotherapy becomes so important.[1] At this point, drugs with a conventional indication for cancer defined by histology and tumor origin lose their importance, giving way to so-called drugs for agnostic tumors, based mainly on the molecular "signature" of the tumor.[4]

In recent decades, increasing knowledge of the human genome and the use of next-generation sequencing (NGS) have had a significant impact on the development of new drugs. However, when it comes to clinical practice, deoxyribonucleic acid (DNA) sequencing has played a supporting role so far, which reflects the limited FDA approvals for complementary diagnostics based on NGS. The trend is for a change in this scenario and the emergence of the first methodologies on the market can already be observed, such as the case of the Foundation One CDx Assay (Foundation Medicine; Cambridge, MA),[1] which is characterized by being a test of comprehensive genomic profile capable of detecting alterations in 324 tumor genes.[5]

Given the scenario of personalized medicine, the optimism linked to its practice, and trends in the future of oncology, there is room for questioning how to bring it ever closer to clinical practice and accessible by the population. This is a recurrent concern of healthcare providers, and the topic was addressed in a dossier prepared by "The Economist Intelligence Unit" in 2020. This dossier established four fundamental pillars for the development of a holistic environment for implementing the practice of personalized medicine, called "The Framework": political governance, awareness and attitudes, infrastructure, and financial management.[6]

In Latin America, in a general context, it is observed that although the political will is still limited regarding the incorporation of personalized medicine, some of its components are common for some countries, although none is complete. Furthermore, healthcare professionals are not fully aware of the potential of personalized medicine and the same happens with patients and their caregivers: the level of understanding of the population is still low, with reservations for specific niches. Finally, the funding pillar was portrayed as the most challenging, as personalized medicine is seen as an expense rather than an investment.[6]

As progress against "The Framework" is uneven for each country, it is difficult to categorize countries based on the metric of "willingness" to adopt personalized medicine in its entirety, so a review of progress and the lack of it without using quantitative parameters (Figure 1).[6]

Tier one countries have substantial elements of the framework in place but are held back by important gaps. They are ***"ready to decide"*** whether they wish to create a comprehensive, holistic approach.

Those in **tier two** have important strengths, but fewer than those in the tier one countries. Accordingly, they need to be in the process of ***"strengthening the foundations."***

Finally, **tier three** states have relatively few assets in place on which personalised healthcare can draw. They are ***"starting the journey."***

Figure 1. Definition of the categories used by "The Economist Intelligence Unit" to group Latin American countries as to the "willingness" to adopt personalized medicine and classification of each country according to the analysis.[6]

According to the article, Brazil falls into the category "ready to decide", being one of the countries with a favorable ecosystem for the implementation of personalized medicine. The country has actions and practices that can serve as a structure for a project with greater solidity, however, it faces obstacles that can hinder the process. The country has a mature health technology assessment (HTA) process and has qualified professionals, but due to the lack of commitment to budget management, there is no commitment to supplying state-of-the-art technologies. As an example, we have the use of biomarker diagnosis in oncology to investigate therapeutic options in the supplementary (private) healthcare system scenario, which unfortunately does not occur in the Brazilian public health system, *Sistema Único de Saúde* (SUS) - in English: Unique Healthcare System. Patients in the public system generally do not have access to genetic testing for oncology and rare diseases because the tests are not formally offered or because in practice the delays are enormous, compromising the patient's prognosis.[6]

Other components involving personalized medicine

Despite having roots in genetic studies, it is important to emphasize that, currently, personalized medicine encompasses much broader components and that all must be considered when determining the best way to treat a patient, such as environmental exposure, developmental phenomena, epigenetic changes, and behavioral factors.[7]

Figure 2, below, illustrates the different factors that should be considered when practicing individualized, patient-centered care.

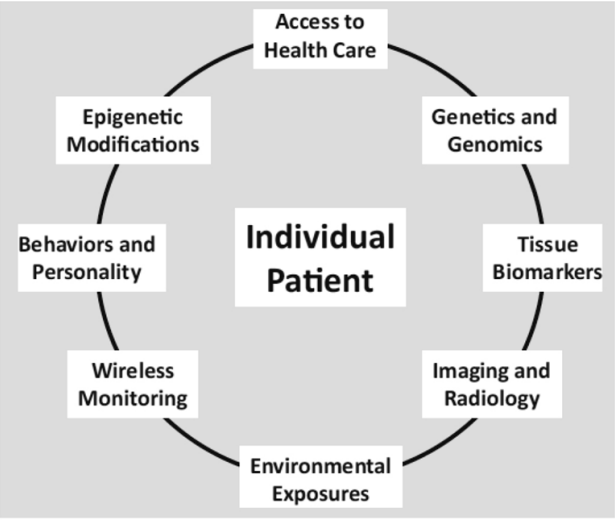


Figure 2. Different components that permeate individualized/centralized patient care currently.[7]

The elements presented must be considered in an integrated and holistic way to achieve personalized medicine. The type of access to health that the patient has is important because some individuals may not be able to obtain knowledge and technologies due to geographic or economic barriers. Therefore, interventions need to be designed for these patients with this aspect in mind.[7]

Genetic inheritance information can be predictive or diagnostic in nature. However, somatic changes in DNA can provide valuable information about pathogenic processes. Tissue biomarkers, such as routine blood tests, are useful for detecting changes in health status, as are imaging and radiology tests, and data routinely collected through remote monitoring.[7]

Environmental exposure and behavioral factors can impact the success of an intervention and exhibit great variability between individuals. Epigenetic phenomena remodel gene function based on different types of exposure and developmental phenomena and should also be monitored as indicators of a change in health status.[7]

Given the definitions, in recent years, numerous technological innovations in the health area are emerging in an increasingly shorter period, raising important issues of financing on the part of health systems. Continuous scientific progress added to resource limitations makes the HTA process an indispensable tool for healthcare managers.[8]

It is also known that the HTA process can be influenced by some interest groups, as: physicians in general, other healthcare professionals, patient advocacy groups, funding institutions, healthcare managers, technology producers, pharmaceutical industries, healthcare service providers, policy makers, and others.[8]

HTA is considered a way of using scientific evidence in the decision-making process for incorporating technologies by healthcare systems. Furthermore, it aims to provide quality information on clinical efficacy, cost-effectiveness, and the scalability of the impact of health technologies to support decisions on the management of health systems.[8]

Thus, to meet funding challenges and adopt smart strategies to broadly serve many patients, the HTA process is used almost worldwide to inform decision-making related to health technologies.[8]

Some countries that are at the forefront internationally and that currently have well-established HTA processes are Australia, Canada, and the United Kingdom. The Australian HTA program, for example, started in the 1980s and was the first country to require cost-effectiveness analysis of incorporating drugs into the healthcare system. The Canadian program began in 88 and the British, in the early 1990s.[9]

In Brazil, Law No. 12,401/2011 represented a milestone in the SUS with the creation of the *Comissão Nacional de Incorporação de Tecnologias em Saúde (Conitec)*

- in English: National Commission for the Incorporation of Health Technologies in the SUS, whose objective is to "advise the Ministry of Health in the attributions related to incorporation, exclusion or alteration, by the SUS, of technologies in health, as well as in the constitution or change of clinical protocols and therapeutic guidelines".[9,10]

Additionally, Conitec is responsible for preparing or changing the PCDT, "documents that establish criteria for the diagnosis and treatment of a disease, with medications and other appropriate products".[11] All approved PCDTs are published on the Conitec website and are made available according to different health conditions.[12] Figure 3, taken from the Ministry of Health's online page, illustrates the incorporation steps defined by Conitec.

The emphasis of this work is the SUS, but it is important to consider that the HTA process is used to incorporate technologies both in SUS and in supplementary health.[8] As it is privately financed, the technologies are usually first made available on the list of the *Agência Nacional de Saúde Suplementar* (ANS) - in English: National Supplementary Health Agency - which undergoes a review every two years, but they do not guarantee that most of the population has access to these technologies.[6]

Data show that more than 75% of the Brazilian population use the SUS as the only way to access treatment for health problems.[6] This percentage by itself already represents the strong need to provide state-of-the-art healthcare, including personalized medicine, to all patients, regardless of the economic potential of individuals.

Also reinforced by the guiding principles of the SUS, established in the Brazilian Constitution of 1988 and by Law No. 8,080/1990, the State must "ensure the population's access to health goods and services in a universal, egalitarian and integral manner".[13] Therefore, considering the best technologies and managing them in the best possible way is a crucial element for the sustainability of the system and the assistance of the population.

Figure 3. Incorporation steps defined by Conitec.[11]

Graph 2 shows the evolution of investments in public health services in Brazil, from 2017 to 2021, according to the Transparency Portal of the Comptroller General of the Union.[14] Despite seeming to be a considerable amount, according to data from the *Instituto Brasileiro de Geografia e Estatística* (IBGE) - in English: Brazilian Institute of Geography and Statistics - spending on healthcare in Brazil represents about 9.2% of the gross domestic product (GDP).[15]

Considering this modest scenario of investment, and the different healthcare needs, many managers consider it challenging to invest in new technologies of personalized medicine in its entirety.[6] It should be considered, however, that Brazil is the largest country in Latin America, with approximately 210 million inhabitants, and it is estimated that cancer will become the main cause of death in the country by 2028.[16] Precisely for this reason, it is urgent to develop long-term strategies and sustainable solutions for the system.[6]

Considering this scenario, the purpose of this work is, through a bibliographic review, to promote the debate on personalized medicine with a focus on oncology, with the recovery of history and an indication of the latest news, in addition to generating discussions for the public healthcare ecosystem considering a challenges x opportunities matrix.

It is also expected to acquire a broad view of personalized medicine and its tools from the perspective of oncology, disseminate the theme, support, and foster initiatives to implement personalized medicine tools in the Brazilian public healthcare system, contributing to a sustainable ecosystem in the incorporation of technologies, and above all, with the health and quality of life of patients.

MATERIAL AND METHODS

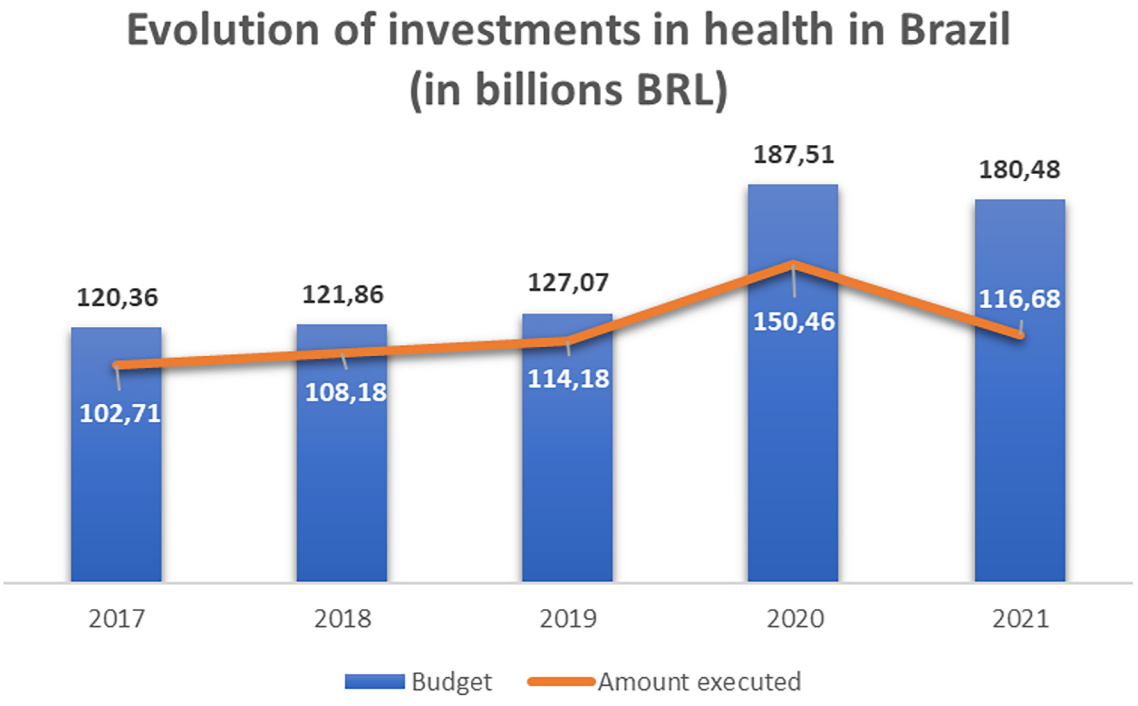
This work is based on literature reviews, with an exploratory and descriptive character, having considered scientific articles related to personalized medicine, oncology, and health technology assessment. The databases used were Web of Science, Medline/PubMed, and SciELO. The following descriptors were used in the search both in Portuguese and in its English counterpart: "personalized medicine", "precision medicine", "oncology", "biomarkers", "health technology assessment", "incorporation of technologies in the *Sistema Único de Saúde* (SUS)", "Brazilian public healthcare system", and "evidence-based medicine".

Articles and scientific journals, in English or Portuguese, with free license or available to the University of São Paulo (USP), which were published in the last 21 years (2000 to 2021), were analyzed. Priority was given to the most recent publications to preserve the contemporaneity of technological innovations related to the subject. Following the search in the databases mentioned above, publications were selected based on the reading of titles and abstracts and later, the full article, if it fit the objective of the investigation.

As exclusion criteria, articles published more than 21 years ago, repeated articles, published in languages other than English or Portuguese or that did not meet the objective of this investigation were used.

RESULTS AND DISCUSSION

Table 2, below, captures the main findings related to challenges and opportunities for the implementation of personalized medicine in the SUS, considering the following topics: technical-scientific aspects, clinical practice, and medical education, and public financing and management.



Graph 2. Evolution of healthcare investments in Brazil from 2017 to 2021.[14]

Table 2. Matrix of challenges and opportunities for the implementation of Personalized Medicine in the SUS.

Challenges	Opportunities
Technical-scientific aspects	
Determining which drugs will work best based on the molecular profile of the patient's tumor is also considered a challenge. Although certain drugs are available in the local market, there is a considerable risk that some are not approved for a particular indication, potentially encouraging off-label prescribing.	Recent technologies have improved the speed and breadth of reading NGS as well as data analytics.
The traditional development of clinical trials along the long path of phases 1 to 3, because the evaluation of targeted therapies for rare mutations can be identified in different diseases.	Creation of a national database of genetic mutations and screening of patients undergoing treatment with targeted therapies to make information available to physicians, payers, the pharmaceutical industry, and regulatory agencies.
Obtaining approval of the use of technologies by regulatory agencies.	National accreditation/certification and quality control programs should be expanded.
Lack of more robust evidence that personalized medicine strategies perform better than traditional medicine strategies.	Establishment of national guidelines for detection, testing, diagnosis, counseling, and surveillance of NGS technologies.
The wide adoption of NGS technologies requires the use of specialized methodologies, as well as the high capacity of the people involved to collect and correctly interpret quality data.	
Aspects of clinical practice and medical education	
There is not a wide acceptance of technologies by different stakeholders such as physicians, healthcare executives, insurers, and patients themselves.	A joint database between public and private institutions should be encouraged for sharing real-world information.
It is necessary to improve the efficiency of the way individuals are characterized, but also the way personalized treatments are designed and controlled for each patient.	Academic institutions and medical associations can collaborate to develop continuing medical education about NGS for healthcare professionals dedicated tooncology. Additionally, similar efforts should be focused on connecting medical professionals and technicians.
The breadth and complexity of the information is a challenge to properly analyze and interpret the information that can inform therapeutic guidelines in clinical practice.	
Public financing and management aspects	
The cost of running tests like the NGS can still be four to five times higher than in high-income countries due to taxes and the high cost of analysis, logistics, and infrastructure.	Brazil is in an advanced status about other countries in Latin America and has the potential to become a reference in the region.
There is a lack of engagement and political will to incorporate personalized medicine technologies.	Challenges can be simplified by engaging government authorities and healthcare managers.
The understanding of the mechanisms, potential, and limitations of personalized medicine is still very low.	The advancement of the latest technologies brought cost reduction compared to a few years ago, although they are still expensive.
	Government-led initiatives to bring different stakeholders together to carry out comparative cost-effectiveness analyzes to better inform resource allocation for cancer care.
	A centralized approach to molecular pathology services could facilitate the feasibility of widespread use in NGS in Brazil. The advantages are in substantial resource savings, specialized personnel, and bioinformatics infrastructure.
	A coherent governance approach is needed to enable simple and rapid implementation of appropriate technologies that benefit the entire population.
	Raise awareness of different stakeholders, such as the public, patients, and administrative and healthcare specialists.
	With a well-established HTA process to guide evidence-based decisions and cost- effectiveness analyses, pricing and reimbursement pathways need to be more flexible, allowing for innovations in payment methods and financing methods.
	Both personalized medicine and the whole healthcare system will benefit from the establishment of a framework.

Since the diagnosis of biomarkers is the main pillar of personalized medicine, in an article published in "The Lancet", in 2019, Santos et al. (2019)[16] consider that due to complex regulatory barriers, costs, need for guidelines for quality control, specialized people, and a robust bioinformatics infrastructure, the wide adoption of NGS technologies requires the use of specialized methodologies, as well as the high capacity of people involved to collect and correctly interpret quality data. As a result, major challenges arise on the horizon both at the technical level and in data interpretation and its clinical application.[16]

Although the challenges present themselves, the authors see Brazil as an emerging potential in Latin America as a model for taking advantage of the opportunities that the wide use of NGS can offer.[16] Agreeing with the report by "The Economist Intelligence Unit", among Latin American countries, Brazil is among the most advanced in the implementation of personalized medicine, even though it has obstacles to be overcome through the engagement of government authorities and managers of the healthcare system.[6] While NGS technologies are crucial tools in identifying clinically actionable genetic variables, the breadth and complexity of information is a challenge to properly analyze and interpret the information that can inform therapeutic guidelines. Furthermore, even when relevant genetic variants are identified, many factors that can affect the patient's response, such as factors intrinsic to drug metabolism, genetic history, and tumor heterogeneity.[16]

Other challenges are related to issues of financing and accessibility. In countries where prices for new drugs are set at launch for the entire duration of the patent, a price that is independent of the drug's benefit for different disease indications, there is a disincentive for the manufacturer to develop a test for a better-defined target population because it can affect sales and profitability. Recent technologies have improved the speed and breadth of reading NGS, as well as data analytics, at a lower price. Despite this, the cost of performing these tests can still be four to five times higher than in high-income countries due to taxes and the high cost of analysis, logistics, and infrastructure.[16]

Determining which drugs will work best based on the patient's tumor molecular profile is also considered a challenge. Although certain drugs are available in the local market, there is a considerable risk that some are not approved for a particular indication, potentially encouraging off-label prescription.[16]

The authors of the same article for "The Lancet" identify opportunities to address the challenges and increase access and use of NGS in Brazil. They encourage different types of government-led initiatives to bring together stakeholders, including public and private payers/funders, academic institutions, the pharmaceutical industry, physicians, healthcare professionals, and patient advocacy groups to conduct cost-effectiveness comparative analyzes to better inform the allocation of resources for cancer care.[16]

The study also calls into question the traditional development of clinical trials along the long path of phases 1 to 3, because the evaluation of targeted therapies for rare mutations can be identified in different diseases. When considering therapeutic approaches, the genetic classification of the tumor does not follow the traditional limits of histopathology and leaves room for a growing trend in the development of tumor- agnostic drugs. There is, then, a modest shift towards the design of more modern clinical trials,[16] such as: (i) basket trials – studies in which target therapies are evaluated in different diseases that have the same molecular change;[17] (ii) umbrella trials – studies in which multiple target therapies are evaluated for a single disease classified into subgroups of molecular alterations;[17] and (iii) adaptive trials – studies whose design allows for modifications in the study itself and/or in the statistical methods after the beginning of the study without compromising its validity and integrity.[18] In this way, the public administration could fund the creation of a national database of genetic mutations and the screening of patients being treated with targeted therapies to make information available to physicians, payers, the pharmaceutical industry, and regulatory agencies.[16]

In addition, a joint database between public and private institutions should be encouraged for sharing real-world information – Real-World Data (RWD) – for storage and analysis. This type of initiative contributes to facilitating the characterization of rare mutations and connecting information regarding the outcome of targeted therapies.[16] Academic institutions and medical associations can collaborate to develop continuing medical education about NGS for health professionals dedicated to oncology. Additionally, similar efforts should be focused on connecting medical professionals and technicians.[16]

National accreditation/certification and quality control programs should be expanded to include molecular oncology testing to ensure quality at all stages of the molecular process, from biological sample preparation to interpretation and reporting of results. Also related to molecular process practices, it is recommended that medical associations join with different partners to establish national guidelines for detection, testing, diagnosis, counseling, and surveillance of NGS technologies.[16]

It is also necessary to consider whether the centralized approach to molecular pathology services could facilitate the feasibility of widespread use in NGS in Brazil. Although factors such as logistics and deficiencies in pre-analytical practices can be barriers, the advantages are presented in substantial resource savings, specialized personnel, and bioinformatics infrastructure. In this way, the country could count on a faster, more accurate, scalable, and possibly more sustainable approach in terms of financing (Figure 4).[16]

In evaluating the other pillars of personalized medicine in an integrated manner, the article by Goetz and Schork, in 2018,[7] considers as barriers to be overcome (i) obtaining approval for the use of technologies by regulatory agencies; (ii) there is not a wide acceptance of the technologies by different stakeholders such as physicians, health executives, insurers and patients themselves; (iii) lack of more robust evidence that personalized medicine strategies perform better than traditional medicine strategies.

Goetz and Schork (2018)[7] argue that the future challenges associated with the personalized medicine reality will not only be to improve the efficiency of the way individuals are characterized, but also the way personalized treatments are designed and controlled for each patient. In line with the "Lancet" article, the authors also argue that data collection should be encouraged, as well as the development of better education and training strategies for physicians and health professionals.[7]

"The Economist Intelligence Unit", on the other hand, interprets that regardless of the forms of development of personalized medicine in the country, such as the gradual incorporation of technologies to meet specific needs or a more general approach, success will come through a "basic support structure", called by the authors of the "Framework".[6] Figure 5 presents the four majors' categories of the Framework and their subtopics:

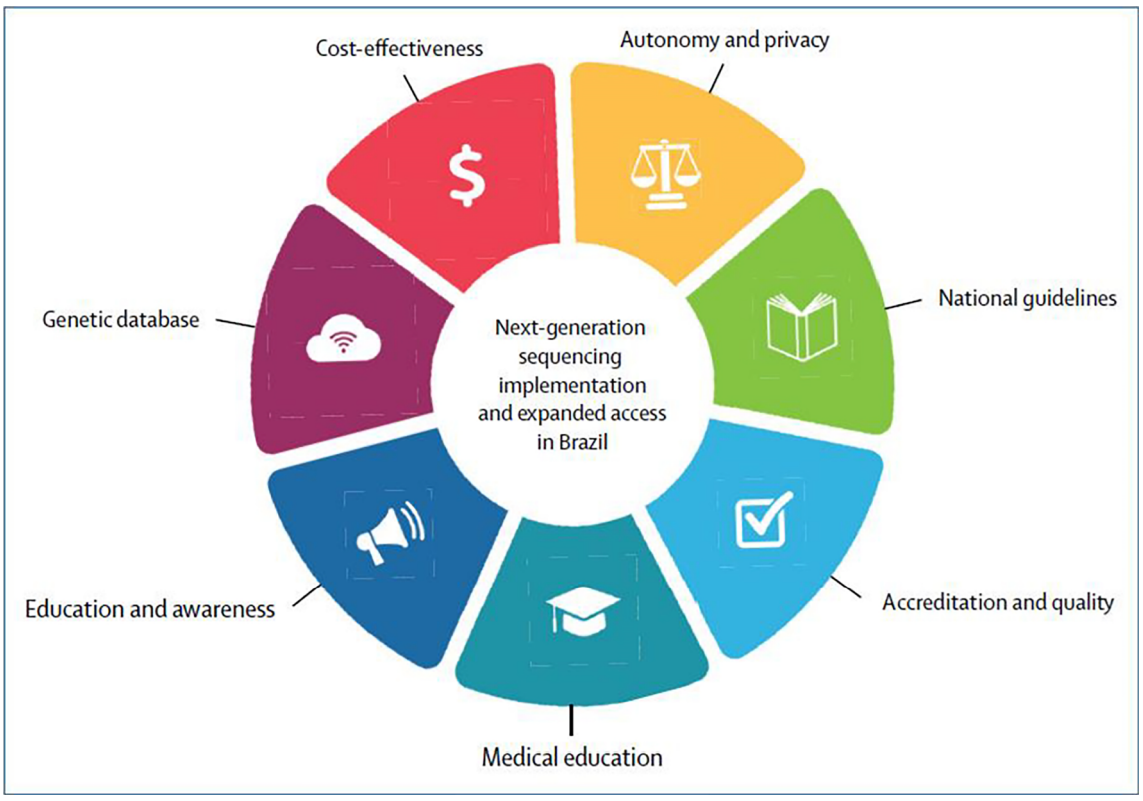


Figure 4. Actions needed to expand NGS adoption in Brazil, according to Santos et al. (2019).[16]

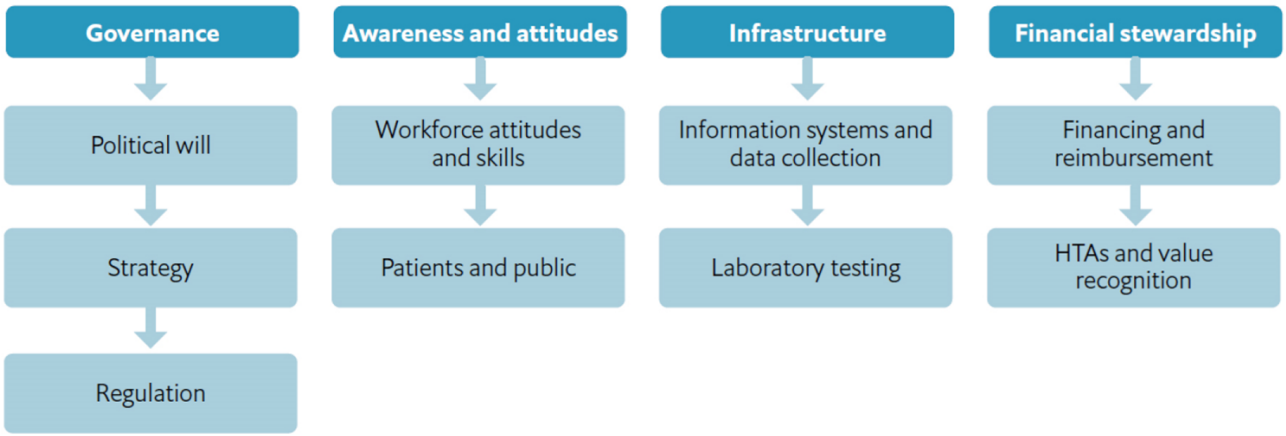


Figure 5. Personalized medicine assessment framework created by "The Economist Intelligence Unit".[6]

The "Governance" category assesses issues of public will, strategic planning, and regulatory oversight. The "Awareness and Attitudes" category assesses aspects of information and awareness of different partners, such as health professionals in general and patients. The "Infrastructure" category evaluates digital information systems, laboratories, and diagnostic services. Finally, the "Financial Administration" category assesses funding and reimbursement issues, as well as HTA processes.[6]

To overcome the barrier of lack of political will, the article argues that a coherent governance approach is needed to allow for the simple and rapid implementation of appropriate technologies that benefit the entire population. As to understanding the mechanisms, potential, and limitations, there is still a way to go to raise awareness among different stakeholders, such as the public, patients, and administrative and healthcare specialists.[6]

From an infrastructure point of view, it will be necessary to improve data collection and processing, and laboratory services to favor and facilitate the adoption of personalized interventions in a faster and more cost-effective way. It will also be necessary to develop areas such as molecular pathology and data science and ensure an information technology infrastructure that allows the sharing of data from different types of records, such as "lab tests, telehealth, remote monitoring, personal devices", etc.[6]

HTA processes are considered of paramount importance in the implementation of personalized medicine. With a well-established HTA process to guide evidence-based decisions and cost-effectiveness analyses, the pricing and reimbursement pathways need to be more flexible, allowing for payment method innovations such as risk-sharing models - sharing agreement risks in the incorporation of health technologies; and alternative financing methods.[6]

Finally, both personalized medicine and the whole healthcare system will benefit from the establishment of a framework as proposed by the authors. "Coherent policies, a better understanding of the public and professionals, improved scientific infrastructure and an effective assessment of health technology" will be useful and beneficial to the entire health system and open the door for new technological innovations.[6]

There is a movement of healthcare authorities to expand the use of personalized medicine in Brazil, a fact that is seen with optimism by specialists in the area. On August 4, 2020, Ordinance No. 1,949 was published, amending Consolidation Ordinance No. 5, of September 28, 2017, to establish the National Program for Genomics and Precision Health – Genomes Brazil and the Council Deliberative of the Brazilian Genomes Program.[19]

In addition to presenting definitions, governance, and financing aspects of the Brazil Genomes Program, the Ordinance establishes that:

> Genomes Brazil is a science, technology, and innovation program whose purpose is: (i) to encourage national scientific and technological development in the areas of genomics and precision health; (ii) promote the development of the national genomic industry; and (iii) establish proof of concept for a line of care in genomics and precision health within the SUS.[19]

The objectives of the Brazil Genome Program address many of the challenges mapped out by researchers in the field and include the establishment of a reference genome for the Brazilian population; the institution of a national database of genomic and clinical information; the increase in installed scientific capacity; the increase in the country's intellectual capital; the strengthening of the national industry of inputs and related products; and the training of the SUS workforce.[19]

As it is very recent, it has not yet been possible to analyze what measures were taken and what results were yielded. It is expected that, with conscientious resource management and actions focused on creating an infrastructure that supports the implementation of personalized medicine technologies, public health management will be facilitated not only in oncology but in the healthcare system as whole. The technologies of personalized medicine may initially seem more expensive,[7] but if well managed and interpreted as an investment, it will bring positive and sustainable results in the long-term for the SUS.[6]

In conclusion, through the construction of a comparative matrix of challenges and opportunities, it was possible to acquire a broad view of personalized medicine and its technologies from the perspective of oncology. It is expected that the theme will be disseminated and may support and foster initiatives for the implementation of personalized medicine technologies in the Brazilian public health system, contributing to a sustainable ecosystem in the incorporation of technologies, and above all, with the health and quality of life of the patients.

The main challenges identified in the different aspects considered revolve around the short "life" of personalized medicine, and therefore they need more robust and conclusive evidence for greater understanding, acceptance, and practice. As these are innovative technologies, the cost is still very high, and there is a lack of specialized personnel to deal with the complexity of the data and generate therapeutic guidelines. It was also verified that there is a lack of political engagement of government authorities and health managers.

Regarding opportunities, it was verified that the implementation of personalized medicine technologies will benefit not only oncology but also the healthcare system will be impacted. As it has a well-developed HTA process in Latin America, Brazil has the potential to emerge as a reference in the region. In the long-term, personalized medicine will bring greater sustainability to the healthcare system in terms of funding providing treatments with greater effectiveness. And as a benefit of personalized medicine itself, its wide adoption in the healthcare system will benefit Brazilian patients, providing a better prognosis for cancer.

It is important to note that the implementation of personalized medicine technologies in SUS is feasible and effective. The scenario is optimistic considering the latest updates from the Ministry of Health with the establishment of the Brazilian Genomes Program. With conscious management of resources and actions focused on creating an infrastructure that supports it, the entire public health system will benefit and benefit from the improvements.

Finally, it is important to mention that personalized medicine is the future of health, although it still has some limitations regarding the number of studies that prove the cost-effectiveness of the wide use of its technologies, opening opportunities for future work in this direction. As Brazil has a well-established HTA process, this type of study can contribute to the incorporation of new personalized medicine technologies in the SUS.

AUTHORS' CONTRIBUTIONS

ACNM: Collection and assembly of data, Conception and design, Data analysis and interpretation, Manuscript writing, Provision of study materials or patient

SSME: Conception and design, Final approval of manuscript

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