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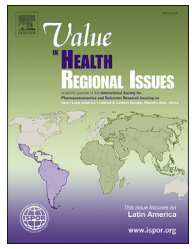

Health Policy Analysis

New Challenges in Oncology for the Brazilian Private Health Sector: Specialists' Concerns After the ISPOR International Congress in Boston, Massachusetts, 2017

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ABSTRACT

The congress of the International Society for Pharmacoeconomics and Outcomes Research is one of the main worldwide forums for the dissemination of research and knowledge on healthcare economics. Brazil is the largest country in Latin America, with a per-capita gross domestic product of $15 200 in 2017 and healthcare expenditure of the order of $1 318 per inhabitant. Brazilian specialists participated actively in the society's latest congress, which took place in Boston, Massachusetts, from May 20 to 24, 2017. They met to discuss the main topics dealt with at the congress and their applicability to Brazilian realities. The topics chosen were precision medicine, new challenges for economic modeling within oncology and immuno-oncology, data to aid in managerial decision making (ie, data from real-world studies), and, lastly, strategies for accessing high-cost medications in Brazil. This opinion article sought to report the main conclusions and consensus reached by this group of specialists on the occasion of this discussion.

Keywords: Brazil, challenges, regulation, reimbursement

Introduction

The international congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) takes place annually. In 2017, it was held for the 22nd time in Boston, Massachusetts, from May 20 to 24. This congress is the main channel for the dissemination of the science of pharmacoeconomics worldwide.

Brazil is the largest country in Latin America, with a population of about 210 million inhabitants and a per-capita gross domestic product of $15 200, according to data available in 2017.[1] Since the time when the 1988 Constitution came into effect, all Brazilians have had the right to comprehensive healthcare through the country's national health system (*Sistema Único de Saúde*), which is the only one of its kind on this continent, funded through taxes and payments from social security contributors.[2] Currently, per-capita healthcare expenditure in Brazil amounts to $1318, that is, just more than 8% of the country's gross domestic product, and this is close to the average for the region. Nevertheless, this figure includes both public and private expenditure and does not reflect the enormous imbalance that exists between these 2 systems. The almost 20% of the population that has access to the private healthcare system spends more than 54% of the aforementioned total, and thus less than half of the total healthcare budget is directed toward the remaining 75% that depends entirely on the national health system.[3] This statistic is an important indicator of the inequality of access to healthcare in Brazil.

The Brazilian private healthcare system is governed by Law 9656, which came into effect in 1998.[4] Since then, all patients who have health insurance have had the right to receive all the procedures that are included in the list of procedures published by the National Health Agency (*Agência Nacional de Saúde* [ANS]), if necessary. This document is renewed every 2 years through a technical analysis process undertaken by a committee of specialists, called the Permanent Committee for Healthcare

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Regulation (*Comitê Permanente de Regulação da Atenção à Saúde*), who are representatives of the various interested parties. For new incorporations, the analysis process takes into consideration criteria such as efficacy, cost, and availability of infrastructure for use of the technology throughout the country. Once a technology is incorporated, its reimbursement is mandatory for every healthcare operator, who are otherwise free to expand their coverage beyond the procedures contained in this list. Nevertheless, the amounts of the monthly subscriptions are adjusted on the basis of this document and thus take into consideration only the new procedures that are included in it. Hence, decisions made by health insurance managers not backed by the national agency cannot lead to possible cost increases to be passed on to insurance users.[5]

The objective of this opinion article, written after participation in the ISPOR event, was to reflect on the topics that were on the event's agenda and that were indicated by 4 Brazilian specialists, representatives of payers in this country, considering the local circumstances, as priorities for the coming years. There was a radiation oncologist, a medical oncologist, a cancer surgeon, and a cardiologist (who is the CEO of a private healthcare plan), all of whom have rich experience in the field. The median time of experience was 20 years, ranging from 10 to 25 years. Almost all the participants reported working exclusively on private healthcare systems; one of them worked in both the private and public sectors. They underwent a phone interview, prior to the panel, to define which topics would be discussed in a 2-hour in loco parentis debate. The chosen subjects were precision medicine, challenges of the "value framework" approach within oncology and immune-oncology, data that may aid in managerial decision making (real-world data), and access to new high-cost drugs (risk sharing). The participants were from different Brazilian regions, representing the South, Southeast, and Northeast regions. The specialists had the opportunity to debate and share their experience and comment on the differences between the Brazilian scenarios. No ethics approval or informed consent to participate was necessary, because there were no patients participating or real patients' data in this study.

A summary of this discussion is presented herein.

Precision Medicine and the Consequences of Its Application Within the Brazilian Scenario

Precision medicine has been described in many ways. For the purpose of this article, the panel has followed the ISPOR Personalized Medicine Special Interest Group designation, which defines it as using genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients with more efficient targeted risk stratification, prevention, and tailored medication and treatment-management approaches.[6] The consensus among the specialists present in this discussion was that Brazilian health insurance managers generally have only a superficial understanding of the concept of precision medicine. There is a lack of in-depth discussion, although they know that this is an important concept, given its widespread and unrestricted dissemination in the lay media.

The concept of precision medicine refers to adaptation of medical treatment to each patient's individual characteristics (phenotype and genotype). Defining exactly which subgroup of patients benefits from a certain drug or technology can be valuable information for regulators, prescribers, and payers. Targeting sensitive patients will, very likely, increase the product effectiveness, or raise the probability of overcoming the cost-effectiveness threshold (whichever it is). Effective biomarkers can also facilitate the earlier selection of alternative and more appropriate second-line treatment options, improving overall effectiveness and, hence, cost-effectiveness.[7,8] The capacity to classify individuals into subpopulations that differ regarding their susceptibility to a given disease is also required. Thus, preventive or therapeutic interventions can be concentrated on those who will benefit from them, while highlighting the expenditure and side effects among those who will not benefit.[9,10] Within the field of oncology, in which the concept of precision medicine is particularly important,[11] the basis is the assumption that one or more molecular alterations may be discovered in a given malignancy. It is becoming increasingly clear that molecularly distinct subtypes exist within various types of cancer, and so different approaches are needed for each subtype. Identifying these aberrations will lead to therapies that are more effective (and, it is hoped, less toxic) in comparison with the traditional exclusively "one size fits all" treatment.[12] The applicability of precision medicine, however, depends on having solid scientific foundations for it. This goal can be trickier than initially thought: most common pathologies, as well as quantitative traits in human populations, have a very complicated genetic basis. The identification of genetic variants that predispose to common illnesses has been troublesome. The missing heritability observed in genome-wide association studies has been attributed to several causes, included rare variants of large effects not detected by existing genotyping arrays, structural variants poorly captured by current technologies, insufficient power to detect gene interactions, and, finally, underestimation of environmental and epigenetic interactions.[13]

Will outcomes improve after the introduction of precision medicine? Which individuals might benefit the most and what harms might come from more routine use of this new technology? Clinical interpretation of genomic tests is challenging even for experts in the field.[14] At this time, these questions remain unanswered, posing a major challenge to those trying to plan the allocation of resources for future care delivery.[15] Within the Brazilian scenario, there has been little discussion regarding the economic impact of using or not using a biological marker that might increase the likelihood of achieving a response to a given therapy. Thus, there is a lack of data that might allow health insurance managers to understand that making use of the concepts of precision medicine has practical meaning. On one hand, they may suspect that use of "companion tests," which are tests that need to be used to identify possible tumor abnormalities in a given patient and hence indicate possibilities for therapies of greater effectiveness,[8] may create a need to use a medication that has significant cost (and which would not have been used if the test had not been performed). Besides, most of the time, such a drug will be available on the local market, but there is a considerable risk that it will not be registered for that indication, which means that it will be necessary to prescribe it off-label, being subject to reimbursement struggles.[14] This cannot be done without clinical validation, which will demand the development of novel methods of efficacy evaluation.[16] Adaptative trials are considered to be a very interesting proposal. An adaptative trial design is an example of innovative effort evaluating targeted therapies. This design allows investigators to analyze accumulating data in prospective interim time points and, if necessary, to change the course of an individual treatment plan, or the trial itself. The appeal of this approach is that it appears that fewer patients would get the inferior treatment.[17] Therefore, multiple questions can be answered in a single study.[18] Some methodological constraints need to be observed though: all adaptations need to be specified before the trial initiation, so that the type I error rate can be calculated, and the probability

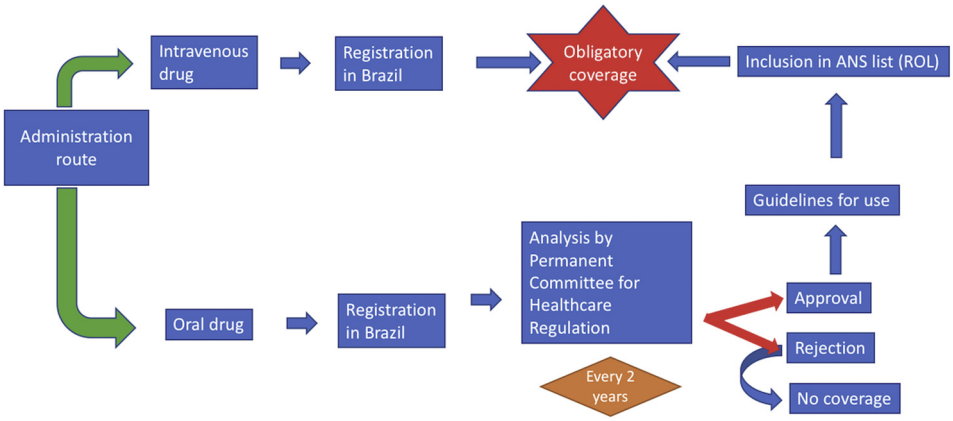

Fig. 1 – Process of incorporation of oncological medications in Brazil in the private sector. ROL: list of procedures of mandatory reimbursement", published every two years by the Brazilian National Health Agency. ANS indicates *Agência Nacional de Saúde*.

of a patient being assigned to 1 arm must remain confidential to maintain its fairness, although changes in randomization proportions may be done (adaptative randomization), in accordance with responses observed, on the basis of a Bayesian probability of better outcome. It is always conceivable that the negative results could be inverted after longer follow-up, in the event of which an arm's low assignment probability would increase, as a consequence.[19]

On the other hand, it remains unclear as to what the cost of simply not doing these tests would be. Not doing them might lead to treatments that are equally expensive but less effective, with an impact on the costs, for example, through development of secondary effects that are potentially avoidable or through unavoidable progression of the disease, with all the tangible and intangible costs that such progression usually involves.[20–22] There was a consensus among panelists that, for Brazilian realities, accessible tests with a high degree of sensitivity and specificity are needed, with the obvious objective of improving the results from treatments, with optimization of the resources used.

It has also been seen that this information is much more useful for health insurance managers before the incorporation of the medication into the therapeutic arsenal available to Brazilian oncologists. Going by Brazilian legislation, a medication that is administered intravenously automatically becomes a part of the obligatory coverage after the medication has been approved and the package leaflet has been made available. Such medications do not need to be clearly itemized on the list of procedures of the ANS. Medications that are administered orally, however, did not form part of the obligatory coverage until only quite recently. Now, they are subject to guidelines for use, drawn up by the ANS. It is not enough to have the package leaflet approved. The process described earlier in the "Introduction" section, with a renewal every 2 years, needs to be followed (Fig. 1).[5] Thus, for medications that are administered orally, the incorporation process is much slower and more complex in the supplementary healthcare market in Brazil. Therefore, information on effectiveness and on cost-effectiveness, if available, may be very useful for health insurance managers, before such medications have been approved. This could favor such medications if they provide cost savings in comparison with intravenous medications. Taking this stance is fully within managers' responsibility and range of actions. This scenario, which is potentially favorable (but contrary to what is stated in current regulations), may be even more favorable for them because it will tend to protect them from judicial petitions, which are filed very frequently within the Brazilian scenario.[2]

This phenomenon of judicialization of healthcare in Brazil began almost 30 years ago when patients with HIV, organized through nongovernmental organizations, collectively demanded free supply of antiretroviral medications from the government. Theoretically, it has been presumed since the 1988 Constitution came into force that healthcare is a duty of the state, or a duty of healthcare insurance, if an individual belongs to the privileged portion of the population that has such insurance. Patients for whom expensive and sometimes experimental medications or innovative technologies have been prescribed seek judicial orders that oblige healthcare managers to buy these medications or to provide elective medical procedures immediately, without previous preparation for this, which brings unpredictability to financial management. Studies have shown that patients mostly win in such cases: there is a strong tendency within the judiciary to accept these petitions.[23] Consequently, managers take up a defensive position, by avoiding expansion of coverage beyond the rigid legal limits that have previously been defined. Judicialization of healthcare tends to disorganize managers' work and hand privileges to those who know how to make demands.

Concluding the discussion on precision medicine, the specialists agree that there is a need to demystify the idea that the pharmaceutical industry manipulates drug prices to compensate for the small number of patients who might use them, through greater transparency in its processes. Considering that with use of precision medicine, only a fraction of the patients with a given type of cancer will have the mutation for which a given medication will provide a benefit, panelists see a considerable risk of increment in price to counterbalance the low level of sales. Studies proving the contrary would be very welcome. It can therefore be seen that Brazilian healthcare managers do not have complete information regarding the price definition process in this country. They are unfamiliar with the government's methodology, which involves a previously defined basket of countries, with selection of the lowest price. Brazilian managers tend to believe that the pharmaceutical industry has greater freedom to set the prices for their products. Greater clarification regarding these processes would be welcome.

Challenges of the Value Framework Approach Within Oncology

In Brazil, payers have been reluctant to adopt formal approaches for healthcare resource allocation decisions, as it has also been seen, for example, in the United States.[24] This is probably because healthcare managers do not have any particular interest in the methodological details of such modeling or in economic analyses of great complexity. Their interest lies in the concepts and results, when there is scientific recognition. Work based on frameworks needs to be stimulated among these professionals, so that the value of a given product can be determined. In this manner, there will probably be greater chances of achieving practical results that provide greater value for patients.

These frameworks need to be patient-centered. Nevertheless, the expectations for such frameworks tend to be detached from reality. An example of this is the classical study by Weeks et al,[25] in which they interviewed 1193 patients with a diagnosis of metastatic colorectal cancer or lung cancer, that is, patients for whom there was no chance of cure through the chemotherapy that had been applied to them, according to the scientific knowledge available at that time. They observed that about 70% of the patients who underwent chemotherapy to treat lung cancer and, even more surprisingly, 80% of the patients with colorectal cancer believed that the treatment they were receiving had the objective of curing their conditions. This lack of clarity regarding the objective of the treatment was seen more frequently among the patients who placed higher value on the level of communication that they had had with their doctor.[25] In other words, patients may blame the messenger for the message and tend to disbelieve this messenger, depending on the scenario, if the message that is received is contrary to their expectations.

This scenario corresponds to the personal experience of those who still practice clinical medicine. The specialists who were present in this discussion added to this through the affirmation that in their experience, patients also do not have any clear notion of the costs of their treatments. They tend to estimate these costs as much lower than they really are. Therefore, information needs to be given to patients in a transparent manner, such that it is complete, clear, and sufficient, so that they have full comprehension. Only in this way can their decisions be adequately valued and considered as their care proceeds. Doctors have a fundamental role in helping them in this regard.[26]

According to the Cambridge dictionary, a *framework* is a support structure around which something can be constructed, which may be a system of rules, ideas, or beliefs that is used to plan or decide on something.[27] Over recent years, various frameworks for cost assessments have been developed as the healthcare system has moved toward an approach that is oriented toward this, that is, concentrating on evaluating therapeutic options on the basis of health and efficacy results, in comparison with other potential treatment options.[28–32] For example, the third section of an ISPOR Special Task Force has identified and defined a series of elements that warrant consideration in value assessments of medical technologies.[24] Nevertheless, the structures that are currently available in Brazil present a wide diversity of approaches, and this inconsistency may lead to varying assessments of treatments. Consequently, there is a need for a robust discussion on relevant perspectives and adequate approaches that would be transparent and methodologically solid, and which would involve participation by the main interested parties, to guide the development of cost assessment frameworks so that healthcare decisions can be made. In addition to patients' central position in this decision making, frameworks need to address 3 key questions, as presented at the congress by Lou Garrison of the University of Washington: What are the cost elements? How are they shown, measured, and validated? How are they used and qualified? In this manner, decisions regarding the costs of treatments can be reached. The cost elements need to be constructed on the basis of the results from cost-effectiveness analyses. There needs to be clarity regarding the perspective that is taken and the context of the specific decision that is to be made, and a structured deliberative process such as multicriteria decision analysis needs to be used.[33]

Although health economists still require results from pharmacoeconomic studies expressed in quality-adjusted life-years, in accordance with the consolidated classical methodology,[34] the specialists feel that it is possible that a paradigm shift is occurring. This is an open discussion, without any certainties regarding its results.[35] The actions of Brazilian health insurance managers have ossified, with rigid regulatory rules and predefined clinical protocols. They are currently unaccustomed to making decisions regarding incorporation of new medications, even though they made such decisions in the past. The actions of directors, managers, and auditors overlap, and this situation varies from one healthcare operator to another. There is therefore a need to communicate with healthcare managers through frameworks, rather than through complex models that ultimately are of no interest to them.

Data That May Aid in Managerial Decision Making: Real-World Data

It is known that clinical trials provide efficacy and safety data about new technologies, but are known, as well, for being inadequate to address real-world decision making, once treatments with demonstrated efficacy based on clinical trials may not be as effective outside the controlled environment of the trial.[36] Nevertheless, real-world data are collected outside a clinical trial and used for healthcare decision making, and can include electronic medical records originated from healthcare providers, data used to coordinate pay for care, and pharmacy data used to fill prescriptions.[37] All the specialists who were present in the panel discussion agreed that real-world data are extremely important for managerial decision making in Brazil today. Over recent years, it has been seen that the number of posters on this topic that have been presented at the congress have been increasing, although no formal count exists, to our knowledge. Real-world data can be understood to refer to data that are gathered within a context that does not comprise a randomized controlled study.[38] Nevertheless, the quality of such data is not always good, within Brazilian realities. The specialists warn that this situation might possibly lead to wrong decisions, with consequent detriment to both healthcare operators and patients.

There seems to be, according to panelist perceptions, a great resistance among healthcare operators with regard to sharing their data, because they tend not to trust those who will use this information. Moreover, at first glance, these operators do not see the potential usefulness of studies that might be developed using such information. A possible interpretation is that they may feel that they will be revealing sensitive core data that might make them vulnerable through exposing confidential information or possible managerial errors. The participants in the discussion stated that operators also feel that even if the possible risks of this type of investigation are mitigated, the data preparation process generates costs and may lead to dissemination of information that, depending on the point of view, may not be concordant with the operator's interest. This is just like what would occur in any private company, which would tend not to release information that might possibly weaken it.

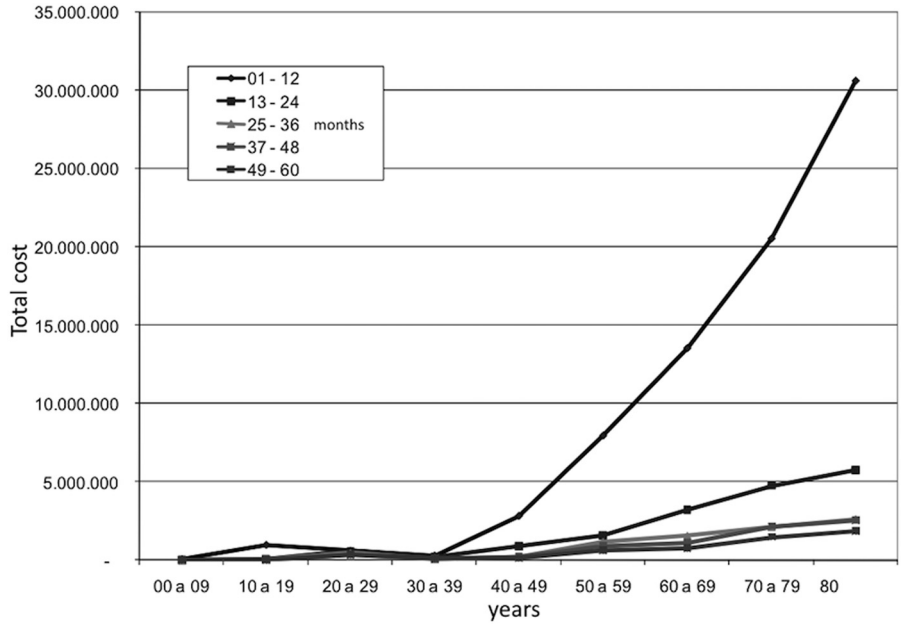

Fig. 2 – Total and relative costs in the months preceding death among beneficiaries of health insurance plans according to age group, 2007-2009. Extracted (with authorization) from Neto.[40]

It needs to be emphasized that, according to the panelists, most Brazilian health insurance managers do not have any training for decision making based on real-world data. For this reason, such results are frequently not used. Thus, they do not discern the opportunity that such data present for improving the outcomes for their operator. For example, according to the panelists, they suspect that this type of study will simply justify new incorporations, with inevitable cost increases, and that they will never be used to propel disincorporation in the event of negative results. In fact, there is a lack of examples of this last occurrence.

In addition to the aforementioned limitations, there is a significant risk that the data may simply be erroneous, because of errors at the stages of data entry, classification, compilation, or any other phase of the complex data production line, starting from the time when the attending doctor fills out forms in the presence of the patient (forms that, according to the consensus, are generally not treated with proper importance) and going as far as compilation of the database.[39] Among the Brazilian operators, there is no systematic cleaning of the information. Once again, this is because this would have a cost implication and, as described earlier, there is no interest in making the data available. The risk of reaching erroneous conclusions is therefore not negligible. This needs to be taken into consideration by healthcare managers who, in the end, decide to use this information. All the specialists in the panel agreed that it was therefore important to demonstrate to those professionals that their operator's real-world data would be useful to them and would in fact improve the quality of their own decisions.[36] Even though changing reality is impossible, knowledge of these realities and their trends may preventively prepare the operator for the future. For example, it has been observed that large sums of money are spent at the end of patients' lives. Real-world data may aid in making a more firmly grounded diagnosis. A study on patients who died between 2007 and 2009, who represented 0.5% of the total number of lives of a self-managed operator (Capesesp), accounted for 22.4% of the expenditure over the study period. Hospital expenditure accounted for the largest proportion of these resources.[40] This information motivated increased investment in palliative care, as a strategy for influencing this trend (Fig. 2).

Access to New High-Cost Drugs: Risk Sharing

The increasing cost of oncological treatment is an evidently highly complex topic. Discussion of this topic and finding viable solutions are necessary and obviously urgent. The prevailing perception is that the problem is serious. Since the law regulating health insurance plans (Law 9656) came into force, there has been a considerable decrease in the number of healthcare operators functioning in Brazil. Hence, there is an urgent need to find one or more effective solutions. Because the coverage that must be offered by healthcare insurance plans in Brazil is rigidly regulated, health insurance managers' room for maneuver lies in the drugs for which coverage is not yet obligatory. Within this scenario, it is important to demonstrate to these professionals what the advantage in expanding their coverage would be.

Various remuneration models are therefore necessary. One possible strategy for maneuvering would be to share the risk. There is a growing interest among payers and producers of medical products for agreements that involve a risk-sharing element. These arrangements involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the amount or level of reimbursement is based on the health and cost outcomes achieved.[41] Risk-sharing agreements place suppliers under an obligation to manage quality criteria and preestablished cost targets that have been agreed on, in exchange for a proportion of the potential savings and, increasingly, the potential financial risk that would result from lack of sharing.[42] Payers have an interest in risk-sharing agreements because they avoid the cost of treatment among nonresponders, require manufacturers to display confidence in their products, allow data on the functioning of a given product in a specific population to be

obtained, and, lastly, enable a focus on quality and demonstration of value instead of focusing exclusively on cost.[43] From the point of view of the pharmaceutical industry, it makes sense to enter into agreements of this nature to accelerate access to markets and obtain competitive differentiation, market-related information, and information on certain subgroups of patients for whom the functioning of the medication is most valuable.[44] Moreover, this would, according to the panelists, deepen the relationship with the treatment funder.

The panelists have different opinions regarding risk sharing, and there has been no consensus on this topic. There are doubts regarding how it could be put into operation. Practical implementation of risk sharing is complex, because it involves a set of logistics insufficiently regulated in Brazil. It would be necessary to define the scenarios within which a risk-sharing agreement might be useful. This is therefore still a nebulous scenario.[45] Other solutions in this regard are urgently needed.

Study Limitations

This article has several limitations. One of the most significant limitations is that the main topics were chosen according to the discretion and experience of the panel members. Although with some punctual coincidences, it did not follow the top 10 health economics and outcomes research trends, defined by ISPOR recently, as the ones that had the most impact in 2018 and the most important to be considered in future research.[46] Another limitation that deserves to be mentioned is that the panel was composed, mainly, of members reporting the payer's point of view. A broader spectrum would, theoretically, have enriched the discussion, with more variated ideas, propositions, and recommendations coming from other stakeholders involved in the Brazilian healthcare sector.

Conclusions

From the data presented, it is concluded that regarding precision medicine, there is a need for clarification of the concept in a more detailed manner for Brazilian health insurance managers. There has been little discussion within the Brazilian scenario regarding the economic impact that its effective application might have. There is a lack of data that might allow those professionals to evaluate whether it has practical relevance, with any potentially favorable cost-effectiveness relationship in its application. There is a suspicion that drug prices might increase to compensate for the small number of patients who would actually use these medications. Solid data on safety and effectiveness, coming from economic analyses, would be highly useful, especially in relation to chemotherapy that is administered orally, before effective incorporation of such drugs into the list of procedures with obligatory coverage that is renewed every 2 years by the ANS.

Regarding economic modeling within oncology, it can be seen that this specialty and its nuances do not merit any special methodology that would be specific to it. Brazilian healthcare managers do not have any interest in elaborate models. There is a need to validate frameworks for Brazilian realities that should address what the cost elements are and how they are shown, measured, and validated; these should be patient-centered. Information that is more complete and as transparent as possible is required. The doctor who attends these patents has the leading role in this regard.

Real-world data are highly important for healthcare operators. Nevertheless, their managers in Brazil are also generally not adequately trained to use these data. It needs to be emphasized that obtaining such information is subject to many risks of significant errors, which would ultimately lead to erroneous conclusions that might impair managers' decision-making process. The possibility of risk sharing is raised as an alternative for the problem of needing to incorporate new medications, with significant costs. Practical implementation of risk sharing is, however, known to be complex and the logistics for its implementation have not been adequately regulated in Brazil.

Thus, the challenges lined up in front of Brazilian healthcare managers are far from small. Nevertheless, tools that may aid them in their work exist, thus making it viable and feasible to furnish healthcare through the Brazilian private system, over the coming years, for the good of its patients, despite the inexorable rise in costs that has been observed in daily practice.

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