



# Brazilian health-care policy for targeted oncology therapies and companion diagnostic testing

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A growing understanding of the molecular pathology of tumours combined with a surge of new drugs and associated diagnostic technologies (ie, precision medicine) has translated into substantial improvements in survival for patients with cancer. However, to achieve the promise that precision medicine has to offer will require overcoming hurdles within a national health-care system in which it is to be implemented. Brazil is one such nation, an emerging middle-income country with a very complex health-care system. To address the challenges associated with implementing precision medicine into a country such as Brazil, a group of experts convened (Nov 16–18, 2015, Miami) to discuss challenges related to precision medicine within an oncology setting. Complex regulatory hurdles, a shortage of human and technical resources, and the complexities of a two-tiered health-care delivery system were all identified as the main shortcomings to effectively implementing this new field of medicine. A path forward was proposed that relies on active collaboration between clinicians, private organisations, and government. It seems entirely possible that, despite many intrinsic economic and political problems, Brazil can readily emerge as a model for other countries in Latin America for the potential benefits of precision medicine and companion diagnostics.

## Introduction

Improvements in the understanding of the characteristics associated with cancer have permitted the identification of the molecular profile of a number of malignancies, which can be used for the development of therapeutic agents specific to that profile.<sup>1</sup> In oncology, precision medicine attempts to combine a patient's medical history, clinical status, and the molecular characteristics of the malignancy to select a therapeutic intervention that offers greater potential for clinical benefit than conventional medicine.<sup>2</sup> The aim of precision medicine is to identify the right intervention for the right patient at the right time, minimising the prescription of costly or ineffective drugs and other interventions, and preventing potentially harmful side-effects. Nearly 30–40% of patients with cancer receive drugs for which the benefit is outweighed by the costs arising from treatment failure or adverse events.<sup>3</sup> For example, in the treatment of colorectal cancer, patients who received cetuximab plus chemotherapy had a better overall response rate than patients who had been given chemotherapy alone, except for those with a particular gene variant (*KRAS* mutant), who did not benefit from cetuximab.<sup>4</sup> Practice guidelines for colorectal cancer now recommend that only patients with a wild-type form of the *KRAS* gene are treated with cetuximab.<sup>5</sup>

The successful use of precision medicine is dependent on the accurate identification of individuals who will best benefit from a given intervention. For accurate identification to occur, diagnostic tests must be used that will correctly identify these individuals. Such tests have been named companion diagnostics.<sup>6</sup> Companion diagnostics provide information that is essential for the safe and effective use of a corresponding therapeutic product.<sup>7</sup> For example, melanoma can be classified by its genetics (eg, *BRAF*<sup>V600E</sup> mutation positive or mutation negative), and lung

adenocarcinoma can be classified on the basis of whether it harbours an *EGFR* mutation or an *EML4-ALK* fusion, or both. Treatments targeting these, and other specific gene mutations, have generated a marked improvement in clinical outcomes.<sup>8</sup>

The promise of precision medicine is not only to provide better outcomes for patients, but also to identify individuals at risk of disease because of a germline alteration, offering the opportunity to focus on prevention or early intervention.<sup>9</sup> For example, women with a germline *BRCA1* or *BRCA2* pathogenic variant, or both, can have up to an 85% lifetime risk of developing breast cancer, and up to a 65% risk of developing ovarian cancer.<sup>10</sup> Testing for *BRCA1* and *BRCA2* mutations can guide preventive measures, such as increased breast cancer screening, prophylactic surgery, and chemoprevention and also identify relatives who might be at risk.<sup>11,12</sup> Of note, the same molecular test is used as a companion diagnostic to select patients for treatment with PARP inhibitors.<sup>13</sup>

Given the rapid emergence of precision medicine and companion diagnostic testing, the Americas Health Foundation (AHF) sought to establish how these new tools can be incorporated into a health-care system such as that in Brazil, specifically in the field of oncology. Brazil is one of the largest countries in Latin America and has a more advanced health-care system than most other countries in the region. Since 1988, Brazil grants free public health care to every citizen. In fact, Brazil's Sistema Único de Saúde—or SUS—has led to huge health gains, including a drop in infant mortality and a rise in life expectancy.<sup>14</sup> Nevertheless, when it comes to the incorporation of high-cost technology, such as molecular tests for cancer, many hurdles can arise. Thus, the country serves as a good model for how precision medicine can be utilised in other countries in Latin America, and the challenges that must be faced to realise all possible benefits.

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## Methods

### Panel selection and consensus methodology

Senior staff of the AHF undertook a literature review to identify scientists and clinicians from Brazil who have published in the field of precision medicine and companion diagnostics with the intention of composing a consensus development panel. Senior staff members of the AHF used PubMed and Embase to identify clinicians and scientists from Brazil with an academic or hospital affiliation, who had published in the field of precision medicine and companion diagnostics since 2010. Augmenting this search, the AHF contacted other individuals in various countries in Latin America and elsewhere to derive a list of individuals from Brazil with the clinical and scientific

expertise suitable for the project. From this list they selected six individuals, representing the disciplines of oncology, pathology, genetics, and applied genomics to discuss the topic of precision medicine. It was important to include a diverse group representing various disciplines related to precision medicine and companion diagnostics. The method used for the consensus development process was based on guidelines from the Consensus Development Conference established by the National Institutes of Health (NIH).<sup>15</sup> Descriptions and recommendations for the use of this method were recently reviewed.<sup>16</sup>

### Questions to be addressed

To better focus the discussion, AHF senior members independently developed specific questions for the panel to address on the basis of the most pertinent issues identified during the literature review. The questions were selected to address the salient issues on the subject of precision medicine. On the first day of the multiday meeting (Nov 16, 2015, Miami) of the panel, each question was discussed at length and an outline for the answer to each question was established. Subsequently, a written response to each of the six questions was initially drafted by one member of the panel, so that before the meeting each member drafted a response to one question. Each narrative was edited by the entire group, through numerous drafts and rounds of discussion. Subsequently, the panel weighed all the information gathered from the round of discussions and reached what was considered a complete consensus statement that addressed the set of four predetermined questions. The consensus statement draft was then presented in a plenary session on Nov 18, 2015, and subjected to review and comment by the panellists. Subsequent to the meeting, the panel was asked to review the document and to again acknowledge that they were in full agreement with the consensus statements. The consensus answers to the following four questions are outlined here, and recommendations on how precision medicine can be more readily implemented into the Brazilian health-care system can be found in the panel.

### What is the use of precision medicine and companion diagnostic testing in the treatment of oncology in Brazil?

Although companion diagnostic testing is available in Brazil, its use is greatly restricted as only a few laboratories have the resources, either human or technical, to do high-quality genetic testing. Additionally, the structure of the health-care system is not conducive to utilising either companion diagnostic tests or their related therapeutic agents, because not all targeted therapeutic agents are commercially available in the country as a result of a delay in oncology drug registration in Brazil compared with the USA and Europe. Payers from both public and private

#### Panel: Recommendations on how to incorporate precision medicine into Brazilian health care

- 1 Health professionals in Brazil with expertise in precision medicine should make a concerted effort to educate their peers on the value of targeted therapeutics and companion diagnostic testing.
- 2 Brazilian public health officials and health-service researchers should collaborate to determine what constitutes a cost-effective treatment, test, or procedure. This effort should be part of an overall increase in health technology assessment.
- 3 Guidelines on the proper use of companion diagnostics and related pharmaceutical interventions should be developed for Brazil. Such guidelines will be of great benefit to ensure that precision medicine achieves its full potential. Medical societies and the Brazilian Government should collaborate in the development of these guidelines, which should be implemented by both the public and private health-care sectors.
- 4 The Brazilian Government should develop a transparent and efficient regulatory process for the approval and use of companion diagnostic tests. In particular, robust quality control procedures and documentation, standardised testing procedures, and programmes are needed to ensure that laboratory personnel are appropriately trained.
- 5 The Brazilian Government should begin the development of nationwide or regional databases that integrate the results of genetic testing with patient-derived demographic and clinical information.
- 6 The Brazilian drug approval process should be streamlined and become more efficient to fully realise the potential of precision medicine to improve the health of the population. A fast track or conditional approval process for a targeted therapeutic that is coupled to a companion diagnostic test should be considered.
- 7 Two separate and dissimilar health systems exist within the country and precision medicine must be delivered within this complex structure.
- 8 The Brazilian Government should make a concerted effort to negotiate the cost of expensive therapeutics so that the price paid for the drug in Brazil is the same as it is in other countries with similar resource constraints.
- 9 The Agência Nacional de Saúde Suplementar should strongly consider updating its list of covered procedures on an annual basis instead of every 2 years. All approved therapeutics and companion diagnostic tests that are considered a standard of care should be approved and reimbursed in a timely fashion.
- 10 Pathologists should be allowed to order and get reimbursed for undertaking genetic tests related to somatic variants.\*

\*Companion diagnostic testing based on germline mutations should always be accompanied by genetic counselling by clinicians with this competency and certification, before and after testing. The public health-care system should reimburse for germline genetic testing, and then also provide genetic counselling. An expansion of existing and the development of new training programmes is needed to increase the number of genetic counsellors.

health-care systems are only required to provide a small number of therapeutic agents, and even for those, the related companion diagnostic tests are not necessarily included in the drug label. Also, in Brazil, there is a marked discrepancy between the tests and treatments available to individuals who receive their health care from the private sector (about 25% of the population) versus the public sector, which all Brazilian citizens have the right to access.

In addition, there is a lack of awareness on the part of health professionals regarding the potential benefits of precision medicine in the treatment of cancer. Precision medicine and companion diagnostic testing requires a multidisciplinary team comprised of clinicians, pathologists, molecular specialists, and others, all working together in a highly coordinated clinical setting. Such integrated teams are generally unavailable in Brazil due to the short supply of both financial and human resources. Finally, although drug approval is crucial, an equally important next step is the commercial availability of these interventions. The pharmaceutical industry can facilitate the commercial availability of these tests and agents by discussing alternative models of pricing of these therapies.

In summary, developing countries such as Brazil should adapt their health-care system to accommodate and make better use of precision medicine and all that it can accomplish in health care. The first step is for health professionals with expertise in this field to educate their peers on all aspects of the subject to guarantee the appropriate use of companion diagnostics. Then, strategies should be designed to bring awareness and education to public and private payers on the potential benefits of precision medicine, to help build the case for improved availability of companion diagnostics and an efficient drug approval process.

### **What are the benefits of targeted drugs in comparison with conventional therapies? What economic factors potentially affect the wider adoption of precision health care?**

Before the last decade, clinicians had little access to technologies that would allow precise predictions about an individual's likelihood to respond to a particular drug treatment. The discovery of predictive and prognostic biomarkers, including the identification of molecular drivers of common cancers, and the identification of different molecular subtypes of several solid tumours, has enabled the development of targeted drugs and better decisions about the most appropriate intervention. However, it is not possible to simply assume that the new precision medicine approach will necessarily be a better option for the treatment of patients with cancer,<sup>9</sup> especially for countries that have very different health-care systems.

The extensive heterogeneity of human cancer should be recognised both between and within different malignancies. In this scenario, it becomes obvious that

generalised treatment approaches will have moderately low efficiency while still presenting substantial toxicity in many situations.<sup>9</sup>

In terms of costs, the economic burden of patients with cancer not receiving optimal treatment worldwide is enormous. Thus, the availability of better patient identification techniques for targeted drug therapies could, in theory, facilitate a more efficient allocation of financial health-care resources. Through accurate selection of patients identified by predictive biomarkers, and earlier initiation of optimal treatments, precision therapeutics has the potential for huge savings, both in terms of cost and patients care. The value of these new strategies must be shown and how elements comprising this value are expected to vary among different countries.

As with any drug, the costs of targeted treatments will depend on the size of the target population—generally, the smaller the population, the costlier the drug. The target populations for precision medicine drugs are, by design, small and selected. Thus, the average annual cost of targeted cancer drugs frequently exceeds US\$100 000 per year.<sup>15</sup> Some authors have suggested that medical care costs will be reduced if precision medicine addresses prevention rather than therapy. However, the very nature of precision medicine, which is targeted, specific, and personalised, might produce interventions that are much more expensive than historically successful preventive interventions that have been applied broadly to certain populations.<sup>17,18</sup>

There are several key examples of the medical benefits of such targeted interventions; however, the true value of these new interventions in comparison with established treatment strategies has often not been properly assessed. Key to the establishment of value are the elements necessary to assess it.<sup>19</sup> One important strategy to address the value of a precision medicine intervention is its analysis in comparative effectiveness research. In this type of research, groups of patients are analysed to compare the effectiveness of alternative therapeutic strategies with the intent of informing clinical decisions and policies affecting health care. Although these studies are becoming increasingly common, we are sceptical of this approach when applied to precision medicine, since patients are grouped together and thus, individual differences could be overlooked. However, an individualised approach to all treatment decisions seems unattainable considering the enormous heterogeneity present in a disease such as cancer and within any patient population.

In addition to the limited knowledge on comparative effectiveness of precision medicine interventions, an additional challenge is the absence of a definition from the Brazilian public and private health-care systems of what is considered a cost-effective treatment or procedure.<sup>20</sup> We encourage widespread discussion of

this issue by health professionals, government officials, and economists so that a consensus can be established regarding the price at which an intervention becomes valuable within a framework of health technology assessment,<sup>21</sup> both in relation to the Brazilian gross domestic product and its health-care resources. The cost of precision medicine (and ultimately its cost-effectiveness) is clearly a limiting force in its adoption and, therefore, cost-effectiveness studies are urgently needed in Brazil to inform decision makers on the potential value of these treatments.

As mentioned earlier, the cost of targeted drug interventions and related diagnostic testing has the ability to reduce overall medical expenditures or increase the economic burden of health care. In Brazil, the government has not yet facilitated the widespread adoption of precision medicine. Although this delay might be due to the obvious concern that such interventions could be too costly, health professionals should still know about the interventions if they are available. Such state-of-the-art medicine might initially have a high implementation cost but could lead to lower health-care costs in the long run, and improve therapeutic effectiveness.

As a result of efforts to translate the concepts of personalised health care into the clinic, precision medicine becomes participatory, and this requires patients to take a more proactive role in their health care. There is value when a patient is integral to the therapeutic decision-making process and therefore feels empowered to influence their health.

The complex challenges in the development of targeted drugs and companion diagnostics, particularly in clinical trial design, suggest the need for a close collaboration among academic institutions, regulatory authorities, and the medical industry. Also, the creation of clear regulatory guidelines that take into account various stakeholder perspectives are crucial to ensuring that companion diagnostics and related pharmacotherapeutic interventions can be used to their full potential.

### What are the regulatory approval pathways in Brazil for oncology-related companion diagnostics and their corresponding pharmacotherapies?

The initial development of a companion diagnostic test almost always occurs in a research setting. Once a biomarker–intervention relationship has been identified and validated, routine testing of patient samples for the presence of an underlying biomarker occurs in both research settings and in clinical laboratories that have the necessary equipment, personnel, and resources for testing.

In Brazil, there is no validated regulatory approval process for a novel clinical molecular laboratory test per se. The absence of any comprehensive regulatory hurdles has resulted in molecular testing that is remarkably free of quality control procedures and documentation, standardised testing procedures, or obligatory certification

systems to ensure that key laboratory personnel are indeed appropriately trained. Additionally, for the most part at least, Brazil does not have the necessary infrastructure to create and manage the data derived from genetic testing. National databases or well-developed information systems that can serve as a repository for laboratory-derived data are not yet widely available. Also, no clinical laboratory information systems or networks exist that can integrate the results of genetic testing with patient-derived demographic and clinical information. All of these shortfalls severely impede, potentially even restrict, the full potential of companion diagnostic testing in Brazil.

Thus, in order to more rapidly implement companion diagnostic testing in Brazil, to maximise its utility, and to achieve confidence in the accuracy of testing, all stakeholders need to make a concerted effort to develop the critical infrastructure needed for effective genetic testing. The development of all of the necessary programmes and procedures can be made easier and no doubt less costly by gaining an understanding of what is now being done worldwide, and tailoring those programmes to the Brazilian health-care system.

Even with a robust system for identifying the underlying genetic cause of a malignancy, the absence of an efficient drug approval process will greatly limit the availability and utilisation of targeted pharmacotherapy. Brazil has a complicated and lengthy drug approval process and a complicated post-approval process that hinders the rapid availability of clinically valuable medications.<sup>22</sup> Although it is laudable that Brazil has invested substantially in expanding access to health care for all of its citizens, the country has, essentially, two clear distinct and dissimilar health systems in the country. The public system allows drugs to become commercially available through processes that are different from those in place in the private health-care system. Of note, the private system, which serves only a quarter of the population, makes up the same proportion of the national health-care budget as the public system, thereby raising questions about the equity in access to health care.<sup>23</sup>

For both sectors, however, the drug approval process is regulated by the Brazilian Health Surveillance Agency/Agência Nacional de Vigilância Sanitária (ANVISA). The approval of a new medicine requires submission of data from well-designed and well-conducted randomised clinical trials that compare the new therapy to current treatment. Besides safety, overall survival and quality-of-life benefits are the key outcomes accepted from phase 3 trials. Unlike the US Food and Drug Administration, no clear mechanism is in place with ANVISA for the simultaneous linking of most companion diagnostic tests with their respective targeted therapeutic drug.

One problem with the design of clinical trials that are used to achieve approval of therapeutic agents is that they require the recruitment of patients with the disease in question who might benefit from the drug in question.

However, targeted therapeutic agents are most likely to benefit a smaller number of patients with a specific genetic variant, who comprise a subset of a much larger population with the malignancy. What would be more desirable are trials that recruit only patients with the genetic profile specifically targeted by that therapeutic agent. Thus, it would be better to do drug approval studies in patients who might be candidates for that treatment.

A limitation of this approach, however, is that to recruit a sufficient number of these patients to prove drug safety and effectiveness, far more time and resources are required. A more efficient system would be to fast track the approval of targeted therapeutics, especially if the drug was coupled to a companion diagnostic test. Alternatively, conditional approval could be granted so that delays in a valuable therapeutic reaching the patient would be minimal. Conditional approval would last for a defined period of time, thereby allowing clinical trials to be completed, and data to become available on the sensitivity and specificity of the companion diagnostic test in a Brazilian population.

Once a drug is approved by ANVISA, the differences between the public and private Brazilian health-care systems become apparent. In the public system, the Câmara de Regulação do Mercado de Medicamentos (CMED) establishes the price of the drug. Although CMED has a transparent system in place to establish a price with drug manufacturers, all too often it is a price too high to be affordable by public-sector hospitals and clinics, and as a result, the drug is not prescribed. Perhaps a better way to derive the price of a drug would be to negotiate agreements with the pharmaceutical industry that mimic the price paid for the drug by other developing countries that have the same resource constraints as Brazil, such as Mexico, Argentina, and South Africa.

After the CMED establishes the price of the agent, the Comissão Nacional de Incorporação de Tecnologias (CONITEC) does an evidence-based analysis to establish the clinical benefit of the drug so that it can be prescribed in the public system. Even if a highly priced drug passes that hurdle, new high-cost treatments are still very hard to incorporate because a fixed amount of money is allocated to patients with a specific diagnosis, regardless of the treatment regimen. A high-cost therapeutic would therefore greatly limit the remaining amount of money available for all other tests and treatments for those patients with that diagnosis.

This environment led to important discrepancies between the public and private health system with a measurable negative impact on patient care. In Brazil, the incidence of breast cancer is more than 50 000 new cases per year, of which approximately 14 000 are HER2 positive.<sup>24</sup> Since 2000, trastuzumab has been approved for use in Brazil. Access to it, however, was restricted to patients able to afford it, either out of their own pocket or through medical insurance policies. In other words, the

vast majority of patients with breast cancer remained without access to trastuzumab for more than a decade due to its high cost. In 2012, however, the Brazilian health ministry granted access to trastuzumab through the SUS, although its reimbursement remains limited to the adjuvant setting.

Despite this move, however, only a few public hospitals have validated in-situ hybridisation techniques for HER2 testing, which limit or delay access to trastuzumab therapy. In fact, in a financially constrained system, a better way to allocate treatment resources would be to calculate the amount provided for the treatment of a disease on the basis of the most appropriate therapeutic option, rather than by using the average cost to treat all patients with a common diagnosis. The table provides a list of companion diagnostics currently reimbursed in Brazil.

In the Brazilian private health-care system, following drug approval by ANVISA, the Agência Nacional de Saúde Suplementar (ANS) will allow a new drug to be used by virtue of a separate approval by the ANS of a procedure relevant to health. These procedures often use drugs as interventions, and therefore the ANS's decisions on these procedures de facto result in ANS approval. Once approved, all private health insurance companies must pay for the drug if prescribed. Of course, the cost of a very expensive drug invariably results in an increase in the insurance premium paid by individuals who want private health care. An increase in premiums might drive those individuals in the private system into the public system, in which a high-cost therapeutic is not available, thereby resulting in a lose-lose proposition for the individual on high-cost drugs. Since the ANS updates their list of covered procedures in only 2-year intervals, the diagnostic and pharmaceutical industries try to prevent delay by approaching health insurance companies and hospitals directly to negotiate the price and availability of their drug or device.

This convoluted system for bringing drugs into market either through the public or private sector shows that there is an urgent need to evaluate and assess the processes in which new therapeutics and diagnostic

	Private health system*	Public health system
KRAS*	Yes	No
NRAS*	Yes	No
EGFR*	Yes	No
BRAF*	Yes	No
FISH for HER2	Yes	Yes

FISH=fluorescence in-situ hybridisation. \*Tests included according to National Agency for Supplementary Health resolution RN-387 from October, 2015. All tests are considered high complexity tests and must be reimbursed as companion diagnostics.

**Table: Tests for listed genetic mutations or HER2 expression that are reimbursed by either private or public health systems in Brazil**

tests become available in the Brazilian health-care system. Therefore, a concerted effort needs to be made to make all therapeutic agents and treatments that are considered to be standard care available to the general population.

### What should the recommendations be regarding the clinical use of oncology companion diagnostics, and who are the policy makers or other organisations responsible for adopting more precision medicine into health care?

The high costs of targeted therapies and molecular testing have substantially increased the cost of cancer care, and it has become an issue in Brazil both for the public and private health-care systems. As more biomarkers are validated and more companion diagnostics become available, procedures and infrastructure will need to be established that are capable of doing tests promptly and efficiently to support timely treatment. In this context, challenges that emerge in the implementation of precision medicine into health-care systems of developing countries, such as Brazil, are multiple.<sup>25–27</sup>

In Brazil, medical oncologists request the vast majority of companion diagnostic tests in oncology practice. Pathologists, generally, are not used to playing an active role in therapeutic decisions, often only reacting to the request of the treating physician. Exceptions are discouraged by the fact that reimbursement might be denied when a pathologist requests additional molecular testing. It is recommended that pathologists be allowed to order and get reimbursed for genetic tests related to somatic variants, to more efficiently obtain test results and thereby initiate treatment faster.

Data generated by companion diagnostic testing can have implications not related to guided therapy. One important example would be the identification of a germline mutation. In that example, ethical considerations, privacy of data, and genetic counselling all come into play, and the appropriate health professionals and procedures should already be in place to achieve the related safeguards and follow-up. Companion diagnostic tests that are based on germline mutation testing should always be accompanied by genetic counselling before and after testing, and thus ordered only by clinicians with this competency and certification. Worldwide, these clinicians include clinical geneticists, physicians with this specific training, and genetic counsellors. In Brazil, only physician clinical geneticists receive this training and are certified, and therefore the private sector only reimburses germline genetic testing ordered by them. On the other hand, the public health-care system in Brazil does not yet pay for germline genetic testing. To expand the number of professionals who are qualified to order these tests and do the appropriate counselling, development and expansion of existing training programmes for other health professionals is imperative to the future development of precision medicine.

Reimbursement for molecular testing in Brazil is still a moving target. Gene-specific tests, such as *EGFR* mutation analysis, and *HER2* amplification testing in the private health-care system, are usually paid for by pharmaceutical companies.<sup>25</sup> This reimbursement has been an important instrument to provide access in the country. However, such reimbursement by pharmaceutical companies should only be allowed upon drug approval and commercialisation in the country, otherwise ethical issues can arise. Starting in January, 2014, health insurance carriers began to reimburse for a specific molecular test and a broader list of tests came into effect in January, 2016. Still, too few tests have been approved and reimbursed, and the time for approval by the ANS takes too long. Change in the approval process should occur more frequently and all companion diagnostic tests should be reimbursed in a timely fashion.

Brazil has an emerging, but very small, molecular diagnostics industry. Most equipment, reagents, and diagnostic kits are imported, thereby increasing costs and limiting access.<sup>25</sup> To speed up the development of a local diagnostics industry and decrease costs, thereby hopefully increasing access, we encourage the ministry of health, funding agencies, and the Banco Nacional de Desenvolvimento Econômico e Social (BNDES) to develop policies and incentives geared towards stimulating the faster development of these industries.<sup>25</sup>

Crucial stakeholders in adopting more widespread use of precision medicine are policy makers, payers, health-care providers, and patient advocacy organisations. Although the use of precision medicine is already a reality and a standard of care in the management of some malignancies, awareness of precision medicine is not widespread in Brazil. Although the ANS has approved a small number of genetic tests for reimbursement, the use of those tests by the private sector has increased slowly; the public sector has lagged even more. In addition to the uptake being slow and clinical criteria for testing incomplete, the Brazilian Government or other health-care organisations have provided no comprehensive regulatory guidance regarding laboratory certification and quality control. We recommend that the appropriate medical and scientific societies develop guidelines and standards for companion diagnostic testing, which should be implemented by the public and private health-care sectors.

In addition, a determined effort is needed to advance health-care professionals' awareness and training regarding the concept, tools, and outcomes associated with companion diagnostics and targeted therapies. This effort should be made at all levels of professional education, including courses in medical school and postgraduate educational programmes. Moreover, if precision medicine is to grow rapidly, Brazil needs more health-care professionals with expertise in this field. Also, professional education for clinicians is necessary so that

### Search strategy and selection criteria

To assist the consensus development panel in their work, the Americas Health Foundation (AHF) senior staff did a careful review of the literature. Papers useful for the consensus discussion and the references cited in this report were identified through searches of PubMed and Embase using the search terms: “precision medicine”, “targeted therapy”, “targeted oncology therapy”, and “companion diagnostics”, searching papers published between Jan 1, 2010, and Dec 31, 2015. Only papers published in English were reviewed. Additional articles were included through the bibliographies of papers identified in the search as well as from searches of the consensus panel members’ own files. Particular attention was paid to papers that reviewed or summarised the topic in question, or if they related to activities in Latin America, especially Brazil. The final reference list was generated on the basis of the relevance to the broad scope of this consensus document. AHF senior staff sought to assemble papers that conveyed a wide variety of viewpoints and perspectives on precision medicine so that panellists had much of the literature at hand to appropriately address relevant issues on precision medicine in Brazil.

they can give technical and clinically relevant information regarding precision medicine to patients and their relatives. Finally, resources are needed to construct nationwide open databases to collect and analyse data generated from genetic and genomic testing. These resources would enable health-care professionals to establish the extent to which the genetic make-up of the Brazilian population influences the response to treatment.

### Conclusion

Over the last two decades, the field of oncology has been marked by the identification of numerous new potential cancer targets and the development of many agents designed to target them. Specific diagnostic tests that facilitate the identification of patients most likely to respond to a given treatment, and the corresponding therapeutic agents that target specific alteration in cancer cells, have ushered in a new era of precision medicine. For Brazil to fully realise the benefits of precision medicine, numerous challenges must be overcome—from the development of the required multidisciplinary teams and associated infrastructure, to a more efficient system to approve and make available new drugs and diagnostic tests, and the need for the Brazilian Government and other stakeholders to understand the value of this new field and how it can help reduce the burdened health-care system. Experiences and scenarios from other countries and regions around the globe facing similar challenges might be useful in facilitating this change.<sup>26–28</sup> We hope that the recommendations outlined in this Policy Review will help Brazil achieve optimum health care for all its citizens.

### Contributors

CGF, MIA, PA-P, MDB, FKM, and SDS contributed equally to the discussion, writing, and revision of the manuscript. CGF did the final revision and submission.

### Declaration of interests

CGF, MIA, PA-P, and FKM report personal fees from the Americas Health Foundation. CGF holds shares in Progenética-Diagnóstico Molecular. The other authors declare no competing interests.

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