Increasing access to next-generation sequencing in oncology for Brazil

A new generation of sequencing technologies has provided unprecedented opportunities for personalised medical care. In oncology, next-generation sequencing can be used to predict disease risk, determine primary tumour molecular alterations, and define resistance mechanisms to therapy. To fully achieve the benefits of next-generation sequencing in oncology, obstacles within the health-care system in which next-generation sequencing is implemented need to be overcome.

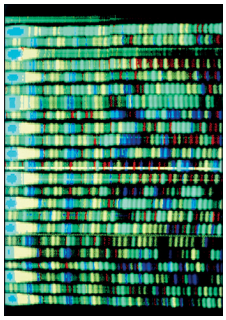
Brazil is the largest country in Latin America, with almost 210 million inhabitants, and it is estimated that cancer will become the leading cause of death in Brazil in 2028. Approximately 630 000 new cases are expected in 2018.[1] Although all Brazilians are entitled

to public health care through its national health system, Sistema Único de Saúde, which is supported by taxes and social security payments, approximately 25% of the population also purchase private health insurance.[2] All patients with private health insurance have the right to undergo all medically necessary procedures included in a list published by the Brazilian National Health Agency. This list is reviewed every 2 years by an expert committee comprised of delegates from several stakeholders, such as medical associations, government, pharmaceutical industries, health insurance, and patient advocacy entities. The committee do a technical analysis to consider criteria such as clinical effectiveness, budget impact, and availability of infrastructure to perform the procedure throughout the country.

Because of complex regulatory hurdles, cost, and the need for quality control guidelines, specialised personnel, and a robust bioinformatics infrastructure, the adoption of next-generation sequencing technologies requires the use of a specialised methodology, as well as a highly trained team, to collect and accurately interpret quality data. As a result, great challenges arise, both at the technical level (as a result of data management and standardisation of quality control), as well as with data interpretation and its application in the clinical setting. Despite these challenges, Brazil could emerge as a model for achieving the opportunities offered by next-generation sequencing in oncology, for Latin America.

To address the challenges associated with the implementation of next-generation sequencing in oncology for Brazil, the Americas Health Foundation did a literature review to identify scientists and clinicians, from Brazil, who have published in the field of oncology and next-generation sequencing. PubMed and Embase were used to identify experts with an academic or hospital affiliation, and who had published in the field of oncology and next-generation sequencing since 2010. As a result of this effort, the Americas Health Foundation identified and convened a seven-member panel of clinical and scientific experts from Brazil that represented the disciplines of oncology, pathology, genetics, and applied genomics. Great attention was paid to ensure recruitment of a diverse group of experts, representing various disciplines related to oncology and next-generation sequencing.

One of the first obstacles of introducting next-generation sequencing into the clinical setting is the uncertainty regarding the interpretation of results and their application in clinical practice. Although next-generation sequencing technologies are a crucial tool in the identification of clinically actionable genetic variants, the breadth and complexity of the information acquired raises new challenges for properly analysing and interpreting the information that can then inform therapeutic guidelines. Moreover, even when relevant genetic variants are identified, there are many factors affecting patient response, such as intrinsic drug metabolism, genetic background, and tumour heterogeneity.[3] Several questions remain unanswered regarding the degree to which the introduction of genome sequencing technology can actually improve patient outcomes, how to identify individuals who might benefit most from these technologies, and how to assess what negative consequences, if any, could result from routine use of this technology. Such questions pose a major challenge for governments and public health officials tasked with planning the allocation of resources for future care delivery.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A second issue involves affordability and accessibility. In countries where prices of new medicines are defined at launch for the remaining patent life, a price that will be independent of the benefit of the drug for different disease indications, there is a disincentive for the drug manufacturer to develop a test for a more well defined target population because this might affect sales. Recent technologies have improved the speed and read length of next-generation sequencing, as well as data analysis, with a decrease in price.[4] Despite this, the cost of doing sequencing tests can still be four to five times higher than in high-income countries because of taxes and the high cost of analysis, shipment, and infrastructure.[5]

A third hurdle relates to privacy and confidentiality. Incidental findings are defined as those concerning individual patients who have potential health or reproductive relevance and are discovered in the course of testing, but are beyond the scope of the study.[6] The ethical implications of informing patients or their relatives about potential risks or genes associated with future disease development must still be defined.[7] The American College of Medical Genetics recently published its recommendations on this topic,[8] and although non-binding, such recommendations are an educational source for medical practitioners; the

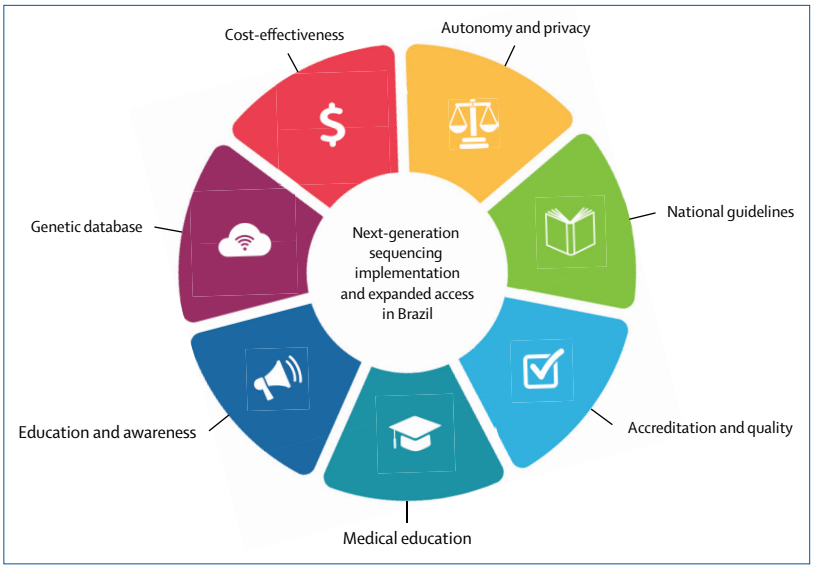

Figure: **Actions to increase implementation and expansion of next-generation sequencing in Brazil**

development of a similar document in Brazil could encourage discussion and debate regarding practical and ethical issues.

A fourth challenge involves determining which drug is likely to work best on the basis of the molecular profile of a patient's tumour. Although such a drug might be available on the local market, there is a considerable risk that it will not be registered for a particular disease indication, potentially encouraging off-label prescription and thus subject to reimbursement limitations.[9]

The panel identified several actions that should be implemented by the Brazilian governmental and scientific communities and non-governmental organisations to address the challenges present in the development and use of next-generation sequencing in oncology for Brazil (figure). These actions include that the government should lead initiatives to bring together stakeholders, including private and public payers, academic institutions, and industry, medical, and patient associations to do comparative cost-effectiveness analyses to better inform resource allocation for cancer care. Evaluating targeted therapies can be a challenge when the mutation in question is rare and is found in several different diseases. The traditional drug approval pathway, involving phase 1–3 trials, relies on large comparative clinical studies and might no longer be the best approach. When considering treatment approaches, genetic classification of a tumour might not follow the traditional limits of histopathology. Furthermore, when tumour development depends on a specific pathway and the targeted therapy reliably inhibits this target, equipoise can be compromised by the possibility of some patients not receiving this specific treatment; thus a traditional randomised trial would not be ethically justfiable. Effectively treating all genetic abnormalities potentially analysed in each patient requires new trial designs and statistical methods, which could drive a shift towards smaller, but more precise, study designs, such as basket, umbrella, and adaptive trials.[10] The government should sponsor the creation of a national database of genetic mutations and targeted therapy agents guided by next-generation sequencing so that patients receiving such therapy can be tracked, with information made available to physicians, payers, drug manufacturers, and regulatory agencies. Collaborative databases should encourage private and public institutions to share real-world data that can be stored and analysed. Such an initiative could facilitate the characterisation of rare mutations and link genomic findings with targeted therapy results. Population-based genomic data should also be included to account for the ethnic diversity of the Brazilian population, which will enable the use of more comprehensive next-generation sequencing panels in the near future. Medical associations and patient organisations should develop education and awareness activities to better inform patients and health-care professionals about the uses, applications, and limitations of next-generation sequencing. Academic institutions and medical associations should collaborate to develop continuing medical education for oncology-related health-care professionals on the use of next-generation sequencing. Additionally, similar efforts should be done by related medical and technical professionals. Existing national accreditation and quality control programmes should be expanded to include molecular oncology tests to guarantee quality in all steps of the molecular process, from sample preparation to result interpretation and reporting. Medical associations should bring together different stakeholders that are related to next-generation sequencing to establish national guidelines for the detection, testing, diagnosis, counselling, and surveillance of next-generation sequencing technologies. Stakeholders should consider whether the centralisation of molecular pathology services could facilitate the viability of next-generation

sequencing in a universal health-care setting. Although drawbacks to this approach include sample transport and ensuring standardisation of pre-analytical factors, next-generation sequencing platforms require substantial capital expense, specialised personnel, and a robust bioinformatics infrastructure, which could make a centralised approach faster, more accurate, more scalable, and possibly more affordable. We must also ensure that patients' autonomy and privacy is protected when performing next-generation sequencing.

All stakeholders need to be aware that new and more effective drugs and treatments could be offered to patients only after scientific research and investment has been made to produce high quality data from clinical trials. Additionally, international collaboration and genomic research expertise will improve clinical knowledge and support the development of scientific capacities for next-generation sequencing technologies.

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