

## REVIEW

# Narrowing the gap of personalized medicine in emerging countries: the case of multiple endocrine neoplasias in Brazil

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The finished version of the human genome sequence was completed in 2003, and this event initiated a revolution in medical practice, which is usually referred to as the age of genomic or personalized medicine. Genomic medicine aims to be predictive, personalized, preventive, and also participative (4Ps). It offers a new approach to several pathological conditions, although its impact so far has been more evident in mendelian diseases. This article briefly reviews the potential advantages of this approach, and also some issues that may arise in the attempt to apply the accumulated knowledge from genomic medicine to clinical practice in emerging countries. The advantages of applying genomic medicine into clinical practice are obvious, enabling prediction, prevention, and early diagnosis and treatment of several genetic disorders. However, there are also some issues, such as those related to: (a) the need for approval of a law equivalent to the Genetic Information Nondiscrimination Act, which was approved in 2008 in the USA; (b) the need for private and public funding for genetics and genomics; (c) the need for development of innovative healthcare systems that may substantially cut costs (e.g. costs of periodic medical follow-up); (d) the need for new graduate and postgraduate curricula in which genomic medicine is emphasized; and (e) the need to adequately inform the population and possible consumers of genetic testing, with reference to the basic aspects of genomic medicine.

**KEYWORDS:** Genomics; Multiple Endocrine Neoplasia; RET; MEN1; AIP; Medical Genetics.

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## INTRODUCTION

The finished version of the human genome sequence was completed in 2003, and this event initiated a revolution in medical practice, which is usually referred to as the age of genomic medicine or personalized medicine (1,2). Genomic medicine aims to be predictive, personalized, and preventive, mostly with regard to mendelian inherited disease forms, but also to complex disorders (3). Further, it must be participative, because patients, their at-risk relatives, and the potential consumers of genetic testing should be aware of the pros and cons of this new technology. Thus, genomic medicine is the art and science of the four Ps (4Ps) (4). The effect of genomic medicine on clinical diagnosis and treatment is currently limited; however, it is almost certain that its impact will increase exponentially in the coming years, as costs of genome sequencing are decreasing rapidly

and may achieve the expected US\$1,000 in the near future. It is anticipated that genomic medicine may help to improve the quality of life and prolong human survival. However, the genetic analyses that have been developed and which have been ready to use for some time now, have been underutilized in the past decade (3). Although the fields of genetics and genomics are well established in developed countries, important progress has been made in other countries in recent years, especially in the emerging countries (5). In order to the increase this development and growth, these countries should immediately begin to tackle essential issues, some of which are discussed below (1-4).

## Reimbursement

A crucial issue is the reimbursement of genetic testing by the health insurance companies. Although the costs of genetic testing are reducing, it remains expensive for most of the population. In addition, an adult positive-mutation carrier may have several at-risk children to be tested. However, extensive data evaluating the economics of genetic testing are lacking (<http://www.genome.gov/19016729>). Hopefully, in the near future, health insurance companies that are established in emerging countries may

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agree to cover the costs of genetic diagnostic testing of their clients, and thus offer this new technology to patients and their at-risk relatives.

### Confidentiality

An important issue is the confidentiality of genetic test results. In 2008, the Genetic Information Nondiscrimination Act (GINA) was approved in the USA. Approval of this law was strongly supported by Senator Edward Kennedy, among others ([http://help.senate.gov/old\\_site/Min\\_press/2008\\_04\\_24\\_a.pdf](http://help.senate.gov/old_site/Min_press/2008_04_24_a.pdf)). GINA is considered to be one of the most important antidiscrimination laws approved so far in the USA. The law has two parts: one that prohibits genetic discrimination in health insurance, and one that prohibits genetic discrimination in employment.

In large areas of the world, genetic testing is not properly regulated. The lack of a GINA-like law in many countries may limit the interest of many healthy individuals and patients in participating in genetic testing. Presently, the approval of such a law constitutes a major challenge to legislators all over the world. The global approval of antidiscrimination laws would constitute one of the bases for a modern and humanized genomic medicine for the 21st century.

However, genetic testing is a fast-growing field and present laws do not cover every situation (<http://health.nih.gov/topic/GeneticTestingCounseling>). A critical issue is the routine inclusion of genetic testing results in a person's medical records, with the possibility that these data may be accessed by employers and health insurance companies. As far as we know, this specific and critical aspect requires further regulation in many countries. A valid approach would be to include genetic testing results in personal records only after obtaining written, specific informed consent from the patient or his/her legal guardian.

### Public and private funding

Public healthcare systems from different countries should consider the potential benefits of funding programs, probably based initially on searching for mendelian germline genetic mutations, such as those occurring in cancer genetics. Extensive data evaluating the economics of genetic testing are needed to give further support to these initiatives. Family screening for mendelian diseases could be the first choice (3). However, large portions of the world's population do not have access to a private healthcare system and cannot afford the expense involved in genetic testing.

It is possible that private groups supplying investment funds may play an important role by supporting small innovative companies who are researching into new and informative genetic tests.

### New medical curricula

In general, medical schools in many countries have not yet developed innovative curricula that introduce medical doctors to the world of genomic medicine. Therefore, there should be a strong effort, particularly in emerging countries, to educate graduate and postgraduate medical students in the rapidly advancing field of medical genetics and genomic medicine. In this century, clinical practitioners will be required to have substantial knowledge of personalized medicine to better manage patients with inherited conditions.

### Information to the community

Finally, the public should be informed about the basic findings and advantages to be gained from the enormous amount of research data related to genomic medicine. This information may bring several benefits. First, it would make it easier for a person to search their family medical history to find out whether there is an inherited condition in the family, facilitate the personal clinical and molecular diagnosis for any affected members, and allow members to take advantage of genetic screening, early diagnosis, and preventive treatment.

This also raises new challenges, however. The US Food and Drug Administration has been investigating how best to oversee and validate direct-to-consumer test kits. There is concern that doubts over the validity of these tests, and inconsistency in results from different companies, may result in a strict regulatory framework that will hamper scientific innovation. *Nature* has examined and reported these issues (<http://dx.doi.org/10.1038/news.2010.382>).

### Genomic medicine in emerging countries: the Brazilian experience

Recently, a series of six papers discussing the Brazilian public health system were published in *The Lancet* (6–10). These papers identified important advances in the Brazilian healthcare system over the past decade, as well as several future challenges in this field. Brazil is presently the second largest emerging country within the BRIC (Brazil, Russia, India, China) countries, with more than 190 million people. However, a large proportion of the population does not have private healthcare insurance, and thus depends on the Brazilian public health system, the Unified Health System (SUS). As a result of the economic stability and growth of the last decade, the Brazilian government is presently funding projects relating to human genetics and genomics. The first whole-sequence determination of a plant pathogen, *Xyllera fastidiosa*, carried out by the Brazilian ONSA (Organization for Nucleotide Sequencing and Analysis) Network, funded by the São Paulo State Research Foundation (FAPESP), was a landmark in genomics science in this country (11). Further investments have been made by FAPESP and the National Research Agency (CNPq) in programs such as the Human Cancer Genome, as well as medical genetics initiatives that are being developed into potential applications in the SUS.

In Brazil, the possibility of applying genomic medicine to clinical practice has not yet had a significant impact. Brazil has achieved substantial economic growth in the last decade. Nevertheless, the vast majority of the population has limited access to modern medicine and especially to genomic medicine, although some initiatives have been performed.

An example of a pioneering initiative is the screening of some of the inherited endocrine neoplasia susceptibility genes (*RET*, *MEN1*, *p27Kip1*, *AIP*, and *TMEM127*). This program was supported by the SUS, through the FFM (School of Medicine Foundation), and partially by FAPESP. We conducted this project from 2000 to 2011 in the largest non-profit academic hospital in Brazil: the Hospital das Clínicas of the University of São Paulo School of Medicine. DNA samples from 871 patients and their at-risk relatives were studied. Informed consent was obtained from all individuals or their parents. DNA from patients diagnosed with multiple endocrine neoplasia type 1 or 2 (MEN1 or

MEN2), familial isolated pituitary adenoma (FIPA), and non-syndromic familial pheochromocytoma (F-PHEO) was genetically sequenced. Out of the 871 individuals, 346 carriers of disease-causing germline mutations and 525 non-carriers were identified (12–26). The positive mutation carriers have greatly benefited from the genetic testing for the five tumor susceptibility genes. Early diagnosis, genetic counseling, and recommendation of appropriate and potentially preventive/prophylactic surgeries have been offered to patients. Consequently, high cure rates have been observed in this group of patients, particularly in *RET*-positive mutation carriers who were genetically detected at an early age (<10 years) (12–15,24). This strategy demonstrated that public familial screening programs, attempting to apply current knowledge from genomic medicine to medical practice, may have a positive impact on the quality of healthcare systems in emerging countries.

The feedback of the referral physicians was positive and demonstrated an evident improvement in their capacity to manage the genetically diagnosed individuals and their at-risk relatives. These results confirm that Brazil needs new medical curricula emphasizing recent advances in the study of the human genomics, proteomics, and many other “-omics”.

In 2009, the integration of genetic medicine into Brazil's universal healthcare system was approved by the government as the National Policy to Clinical Genetics Care (<http://www.in.gov.br/imprensa/visualiza/index.jsp?jornal=1&pagina=50&data=21/01/2009>). Under this law, public healthcare systems and private insurance companies are requested to reimburse a limited amount of genetic testing. However, the implementation of this law requires regulation. Its final approval/regulation will be welcomed, as there will be better medical care for patients and their at-risk relatives.

In conclusion, genomic medicine should be predictive, personalized, preventive, and participatory. It has been implemented mostly in developed countries, and several issues remain in applying genomic medicine to clinical practice in emerging countries, such as Brazil. However, this needs to be achieved quickly in order to patients take advantage of this era of evidence-based molecular diagnosis. The effort is worthwhile; after all *Whoever saves a life, it is considered as if he saved an entire world* (Mishnah Sanhedrin 4:5). If the purpose of applying the accumulating data from genomic medicine to clinical practice in emerging countries is achieved, it will be another step in reaching the main goal of medicine – to save lives.

## ETHICS APPROVAL

The genetic studies described here were approved by the institutional ethics committee (Cappesq – HC-FMUSP).

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## AUTHOR CONTRIBUTIONS

Toledo RA, Sekiya T, and Longuini VC designed and performed the experiments, and analyzed the data. Lourenço DM Jr, Coutinho FL, and Toledo SPA contributed to the clinical information and discussion. Toledo RA wrote the paper. Toledo SPA was responsible for critical revision of the manuscript regarding intellectual content.

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