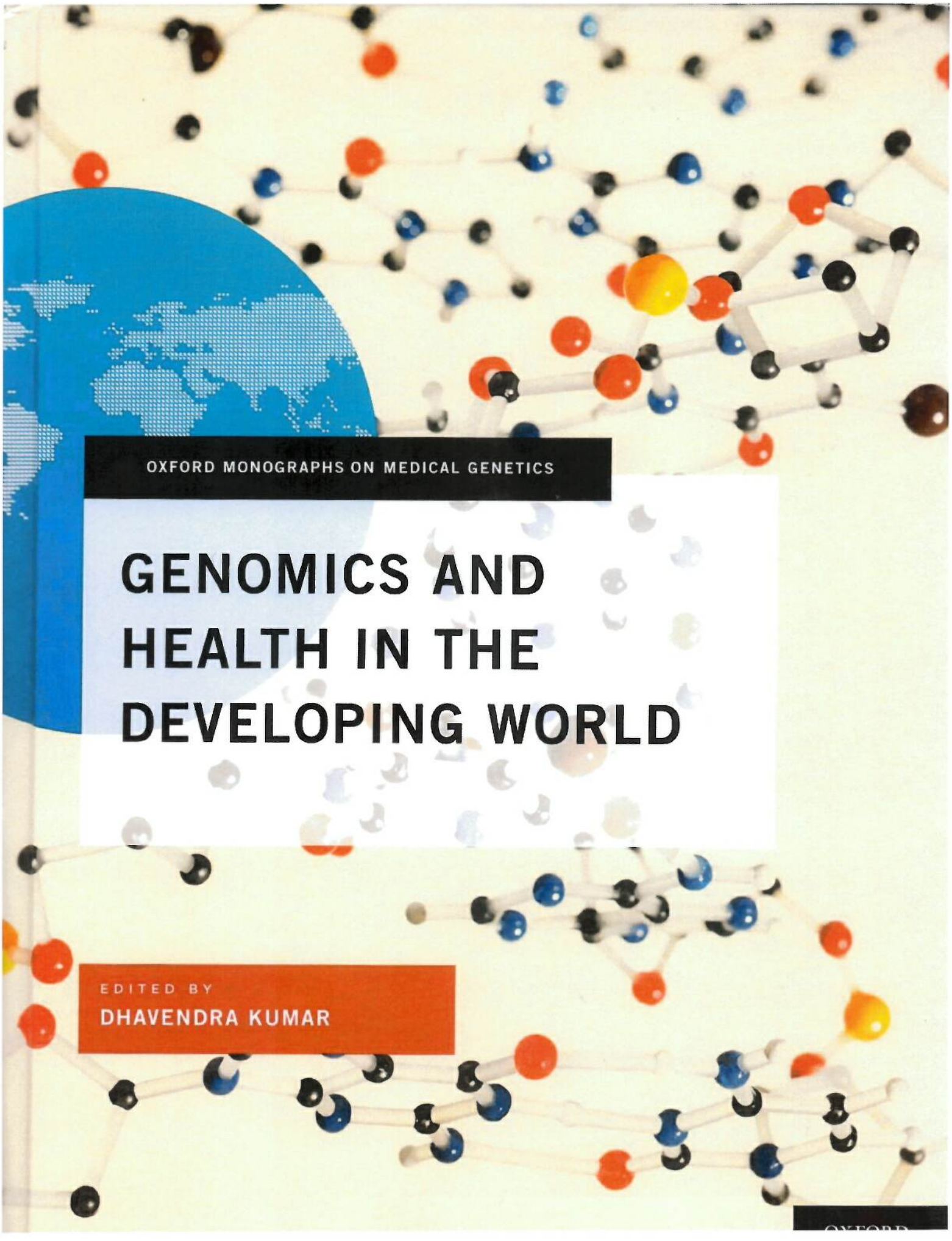
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DESIGN AND IMPLEMENTATION OF A PLATFORM FOR GENOMIC MEDICINE IN MEXICO

Gerardo Jiménez-Sánchez, Julio Frenk, and Guillermo Soberón

INTRODUCTION

The spectacular progress in biochemistry, molecular biology, genetic engineering, and biotechnology that occurred during the second half of the twentieth century paved the way for the sequencing and mapping of the human genome. Genomes contain all of the information needed to determine the functions of an organism and maintain homeostasis, a state of equilibrium within an organism's internal environment. The healthy state depends on the correct functioning of the genome in interaction with the environment. Because of these homeostatic systems, organisms can dynamically adapt to changes in the environment. When this equilibrium is disrupted, disease occurs.

The Human Genome Project (HGP) represented a milestone in human history, not only because of its scientific and technological scope but also because of the great impact that this information will have on people's daily lives. Knowing how variations in the genome confer human individuality will be of great use in medicine, giving physicians the ability to prevent, diagnose, and treat common diseases (Childs et al., 2001). Moreover, the rise of genomic sciences has propelled the development of new technologies to sequence and study the human genome and that of many other species. These technologies have led to novel and more sophisticated opportunities for economic growth through the development of new products, the creation of new intellectual property, commercialization, and identification of new markets. However, these discoveries also pose important ethical, legal, social, political, and even religious challenges that demand adaptive changes in contemporary societies. Thus, it is of great importance that all members of society understand the opportunities and risks that this information generates, so that necessary actions can be implemented to allow equal access to medical applications while preventing inappropriate use of information, thus complying with universal principles related to human rights and respect for societal values (Jiménez-Sánchez, 1999).

The analysis of the results from the HGP has increasingly made evident important differences between traditional genetics, which studies individual genes or relatively small groups of genes, and genomics, which is dedicated to the comprehensive study of genomes with a global focus that covers all the genes in a species. Research in this field has become increasingly focused on understanding the function and regulation of each gene and its interactions with other genes and with the environment.

In February 2001, the first "draft" of the human genome was published. The results of the HGP, supported by the United States government, were published in *Nature* (Lander et al., 2001). Simultaneously, the sequence resulting from the private project by Celera Genomics was published in *Science* (Venter et al., 2001). In addition to mapping and sequencing of the human genome, these projects have produced the first analysis of the genome's contents. Thus, to systematically identify genetic variations in the human genome, a new project was developed: the "HapMap." Its main goal was to describe the most frequent genetic variations in the genome of three ancestral populations: European, Asian, and African. This project successfully concluded in 2006, providing a series of fundamental tools to contribute to the identification of the genetic bases of common diseases (HapMap, 2005). This and other subsequent projects, including ENCODE and "The 1000 Genomes" (Kaiser, 2008), have significantly improved our knowledge of genetic variation and have contributed to the identification of disease-associated genes.

The human genome contains variations in its sequence, the combinations of which confer individuality to each member of the human species. All the members of our species share around 99.8% of our genome. However, there are different kinds of genetic variation in the human genome. Among these, there are between 3 to 10 million single nucleotide polymorphisms. If we calculate the number of possible combinations of these, and other variations also available in the human genome, it will become

clear why each individual has his or her own genetic combination, accounting for about 0.1% of the total sequence. The ability to uniquely identify each individual will have applications in different areas. In fact, in some countries, DNA banks are being developed to identify individuals based on currently known polymorphic variants.

In addition to the complete sequence of the human genome, a map that contains around 23,000 genes and a catalog of more than 1200 genes associated with diseases (Jiménez-Sánchez et al., 2001a) and genetic variations were published. These variations include single nucleotide polymorphisms (SNPs), copy-number variations (CNVs), duplications, and deletions (Iafrate et al., 2004; Wakeley et al., 2001).

IMPLICATIONS FOR HEALTHCARE

Genomic medicine, defined as the analysis of genetic variation to identify risks for common diseases, will lead to a more individualized, more predictive, and more preventive medical practice based on the genetic protection or risk conferred by each individual's genome. Thus, to develop specific applications to diagnosis and treatment of human disease, it is necessary to identify genetic variants associated with common disease risks (Jiménez-Sánchez et al., 2001a).

Our ability to analyze the whole human genome and associate genetic variations to common traits makes an important distinction relative to traditional human genetics approaches, although both disciplines can complement each other to achieve their own goals. Applications derived from the human genome will offer new forms of prevention, including the ability to develop presymptomatic identification of individuals at risk. This may lead to new strategies to influence individuals' lifestyles as part of their primary healthcare.

Overall, genomic medicine has the potential to prevent or delay the presence of common diseases in humans. As a result, it is not too bold to anticipate that, within a few years, clinical medicine will be increasingly immersed in the interpretation of genomic findings and in the design of programs to optimize healthcare of individuals based on those findings.

One of the benefits derived from genomics and proteomics is the ability to design new pharmaceutical drugs based on the identification of their molecular targets and their regulatory mechanisms. Furthermore, it will make it possible to identify those individuals likely to have unusual responses to certain drugs, leading to a safer use of them (Jiménez-Sánchez et al., 2002c). Thus, pharmacogenomics studies the response of individuals to pharmaceutical agents based on the characteristics of their genome (Evans & Relling, 1999; Emilien et al., 2000; Sadée, 1989). Its development potentially will lead to the design of products directed to population groups that share specific DNA sequences associated with better medical effects and less toxicity.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

The use of genomic information may have implications of great individual and social relevance. There are important ethical, legal, and social issues related to the use of genomic information, which contemporary societies need to address in a timely way (Jiménez-Sánchez & Lara Alvarez, 2007). Some of the most relevant challenges include prevention of stigmatization and discrimination of individuals based on their genomic makeup. This includes fair use of genetic information by insurance companies, employers, the legal system, schools, and other institutions. It is therefore important to develop regulatory frameworks that regulate access to this information, among other issues.

Thus, it is essential that the study of the human genome and the development of medical applications be undertaken under ethical principles that will allow societies to benefit from these new opportunities, as well as to avoid the risks of misuse, ensuring respect for the rights and dignity of individuals.

UNESCO produced a "Universal declaration on the human genome and human rights" during the 29th meeting of its General Assembly in November 1997. This declaration, unanimously approved by 186 United Nations member countries, indicates that "no research or research applications concerning the human genome...should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people."

Research on this topic has received worldwide attention. In Mexico, investigators from the Center for Interdisciplinary Studies on Health and Law (http://www.juridicas.unam.mx/invest/areas/neisd/) at the Research Institute of the National Autonomous University of Mexico (UNAM) have worked on different aspects of the legal and social implications of genomic research and have made important contributions to this field (Muñoz de Alba, 2002).

In addition, Mexico has a National Commission of Bioethics that analyzes such challenges in the context of universal principles and national legal frameworks. This commission acquired the status of a decentralized agency of the Mexican Federal Government in September 2005. Recently, it has been provided with growing resources to undertake an ambitious program, which includes studying the ethical, legal, and social aspects of genomic medicine.

HUMAN GENETICS IN MEXICO

Mexico has a solid tradition of biomedical and health sciences, upon which it is possible to construct the basis for

genomic medicine. The disciplines of human genetics, biochemistry, molecular biology, microbiology, immunology, biotechnology, neuroscience, pediatrics, internal medicine, and geriatrics are all mature, and they constitute indispensable elements to the development of genomic medicine research and its applications to public health.

The study of human genetics in Mexico is a relatively recent development; it was only at the end of the 1940s that the first publications of Dr. Mario Salazar Mallén described the distribution of blood types among the Mexican population. In the 1960s, the first genetic research groups were established in hospitals both in Mexico City and Guadalajara. Soon after, the Mexican Association of Human Genetics emerged, along with human genetics as a specialty of medicine at the National Medical Center of the Mexican Institute of Social Security (IMSS) and the Mexican Board of Human Genetics.

Since its foundation in Mexico, human genetics has achieved significant progress in different areas, such as clinical practice, cytogenetics, population genetics, biochemical genetics, neonatal screening and, more recently, molecular genetics. The most relevant contributions of Mexican geneticists are discussed in three publications compiled by Kofman-Alfaro et al. (1991), Salamanca and Armendares (1995), and Lisker and Carnevale (1995). The groups that were progressively established during the last decades have made contributions to scientific research, healthcare, and higher education.

Human genetics in Mexico is a highly decentralized discipline resulting from the establishment of groups of geneticists across the country. Most of these scientists have made important contributions for which they have received international recognition. In the last years, not only have clinical geneticists been trained, but also doctoral programs have produced graduates in the field.

GENOMIC SCIENCES IN MEXICO

During the last decade, the Mexican government has strengthened its commitment to improving competitiveness and innovation through science and technology. Although investment in this area has been consistently limited, from 1995 to 2005 the percentage of the gross domestic product (GDP) devoted to science and technology increased from 0.35% to 0.43%. The number of students registered in doctoral programs in science and technology increased from 488 in 1994 to 2009 in 2005. From 2001 to 2005, the number of researchers in the National System of Investigators increased by 62% (Triunfol, 2007). In addition, in 2002, the Chamber of Deputies of the Mexican Congress approved a new Law of Science and Technology, through which new funding sources, known as the Sectorial Funds for Science and Technology, were established. These funds are composed of equal contributions from the different secretaries (departments), states, districts, and the National Council of Science and Technology (CONACYT).

Mexico currently has more than 12,100 researchers registered in the National System of Investigators. Among them, 24.5% are established at UNAM, and the rest are at public state universities throughout the country. In medical research, the National Institutes of Health (NIH) have about 500 researchers (4.1%), the Mexican Institute of Social Security has around 294 (2.4%), and other areas in the health sector have 87 researchers (0.7%). The fields of biology, chemistry, medicine, and health sciences contribute with 26.7% of the total, reflecting a sustained increase during the past ten years (CONACYT, www.siicyt.gob.mx). Overall, the number of investigators continues to increase, as well as the number of areas in which they work.

In the past 15 years, Mexican investigators have made initial contributions to genomic sciences. These include participation in the genome project for *Escherichia coli* (Blattner et al., 1997) and the first large-scale sequencing project in Mexico, the sequencing of the genome of *Rhizobioum etli*, conducted by the Center of Genomic Sciences (CCG; www.ccg.unam.mx), formerly known as the Center for Research in Nitrogen Fixation (CIFN; Gonzalez et al., 2006), at UNAM. These and other projects have led to a series of genomic initiatives related to different organisms, including the parasite *Taenia solium*, whose genome is also currently being sequenced at UNAM (Aguilar-Diaz et al., 2006). Other projects include the sequencing of plant species, which is mainly being undertaken at the Center of Research and Advanced Studies (CINVESTAV) of the National Polytechnic Institute (www.cinvestav.mx). Recently, the National Laboratory of Genomics for Biodiversity (LANGEBIO) was created with the goal of carrying out important genomics projects in plants, such as the sequencing and functional analysis of the genome of maize. Additional infrastructure for genomic research is located in the states of Guanajuato, Nuevo León, Jalisco, Tamaulipas, and Yucatán, among others (Jiménez-Sánchez et al., 2008).

In 2004, an undergraduate program in genomic sciences (LCG) began at UNAM (www.lcg.unam.mx) at the CCG and the Biotechnology Institute in Cuernavaca, Morelos. The curriculum includes intensive education in mathematics, statistics, computational sciences, and biology (Palacios & Collad0-Vides, 2007). In recent years, two new scientific societies have been founded: the Mexican Society of Genomic Sciences (http://smcg.ccg.unam.mx/) and the Mexican Society of Genomic Medicine (www.somegen.org.mx), with the latter headed by Gerardo Jiménez-Sánchez as its founding president. These societies gather together the majority of scientists who work in the field of genomics in Mexico.

FROM HUMAN GENETICS TO GENOMIC MEDICINE

Mexico has a long tradition in the biomedical sciences and health. Currently, there are more than 250 professionals registered with the Mexican Association of Human Genetics, and more than 175 certified geneticists registered by the Mexican Board of Human Genetics. A variety of institutions together offer more than 50 formal, independent graduate programs in human genetics and molecular biology. As a result, independent research groups have been established in areas that include clinical genetics, cytogenetics, genetic epidemiology, population genetics, inborn errors of metabolism, neonatal screening, genetic toxicology, and molecular genetics (Salamanca & Armendares, 1995).

Historically, the majority of important contributions in genetic research by Mexican-Americans have occurred outside of Mexico, and some contributions have resulted from the collaboration with Mexican researchers. In Mexico, the majority of studies related to the genetic basis of complex diseases have primarily analyzed known variants in candidate genes. Initially, such studies included the association of the HLA-B27 allele with ankylosing spondylitis (Fraga et al., 1979) and the association of other HLA alleles with rheumatoid arthritis. Since then, researchers have described associations between HLA alleles and various complex diseases common among Mexicans. These diseases include type 2 diabetes mellitus and some of its complications (Perez-Luque et al., 2003), generalized lupus erythematosus (GLE; Bekker-Mendez et al., 1998), scleroderma (Vargas-Alarcon et al., 1995), and type 1 diabetes mellitus (Gorodezky et al., 1995).

Other complex diseases have also been studied using candidate gene approaches. Some examples include the analysis of SNPs in the genes encoding insulin, and others associated with different abnormalities in serum lipid levels (Sanchez-Corona et al., 2004), such as hepatic nuclear factor 4-alpha (Weissglas-Volkov et al., 2006), tumor necrosis factor-alpha (Parra-Rojas et al., 2006) and *ABCA1* (Villarreal-Molina et al., 2007). In addition, there have been associations described between GLE and polymorphisms in *PTPN22* (Baca et al., 2006) and *PCDC1* (Velazquez-Cruz et al., 2007) in children, as well as between GLE and polymorphisms in *PCDC1* in adult patients (Prokunina et al., 2002).

The 677C>T polymorphism in the methylenetetrahydrofolate reductase gene (*MTHFR*) is associated with diseases related to hyperhomocysteinemia and folate deficiency. It has been found that, among Mexicans, the 677C>T allele is weakly associated ($p = 0.05–0.01$) with hyperhomocysteinemia (Torres-Sanchez et al., 2006), anencephaly (Munoz et al., 2007) and gastric cancer (Lacasana-Navarro et al., 2006).

The analysis of genetic variations related to pharmacological responses has mainly focused on the genes that encode for metabolizing enzymes, such as *CYP2D6* (Contreras et al., 2011; Hidalgo-Miranga & Jiménez-Sánchez, 2009). In the case of this gene, the allelic frequencies show significant differences among the different populations of Mexico. For example, *CYP2D6*10* has a frequency of 12.45% among individuals in Mexico City (Lopez et al., 2005) and a frequency of only 2.3% among individuals in the north-central state of Durango (Sosa-Macias et al., 2006).

Clearly, Mexican geneticists have achieved important milestones; however, to identify novel genes associated to common diseases in Mexicans, it is important to implement modern research strategies such as genome-wide association studies (GWAS), dense genotyping, and resequencing approaches, among others, to achieve an emergence of research in genomic medicine.

Genomic analysis of cancer in Mexico is currently undergoing a transition from the classic genetic approaches to whole-genome analysis, including whole expression and copy-number variations analyses (Hidalgo et al., 2005; Valladares et al., 2006; Vazquez-Ortiz et al., 2007). This is transforming the area of molecular oncology in Mexico, particularly in cervicouterine and breast cancers.

To further develop human genetics and genomic medicine in Mexico, new experimental designs are required, including those considering the genetic structure of the Mexican population, supported by the collection of large numbers of disease-specific samples. In addition, training a higher number of health professionals in genomics and public awareness programs are needed so that Mexico takes full advantage of genomic medicine.

DEVELOPMENT OF GENOMIC MEDICINE IN MEXICO

Genomic medicine will allow for more individualized, thus effective, interventions. These will need to be incorporated into health policies to turn medical practice into a more individualized, predictive, and preventive discipline. Thus, scientific research must be a priority to identify disease-associated genetic variants in the Mexican population. Currently, an important number of genetic variants have been identified for various common diseases, including diabetes mellitus (Wellcome Trust, 2007; McCarthy, 2010), cardiac diseases (Wellcome Trust, 2007), Crohn's disease (Mathew, 2008), and various types of cancer (Easton et al., 2007; Zanke et al., 2007). This information, and its corroboration in different populations, has the potential to strengthen screening programs, diagnostic and prognostic strategies, and the identification of new therapeutic targets and novel molecules of pharmacological use. Such strategies would not only decrease chronic complications and their associated costs, but can also

improve medical care and the patient's quality of life, and lead to a more rational use of health resources and better-supported decisions in public health (Jiménez-Sánchez et al., 2001b).

Many believe that the main challenges that Mexico faces can be divided into two categories: on one hand, overcoming painful lags in development that work against the dignity of its people, and on the other, the capacity to develop strategies to join emerging opportunities at the frontier of science and technology for the benefit of its people.

The challenges that a country must face in relation to its economic and social development are many and varied. There are pressing problems that will be overcome in the midterm and long term future. However, we have learned that challenges should not be dealt with in chronological order. Thus, it is not valid to suggest that Mexico should not embrace the emerging frontiers of science and technology to improve healthcare and wellbeing until previous, pressing challenges are solved. In fact, overcoming current hurdles and embarking upon promising new paths should be done simultaneously. As such, it is universally recognized that economic and social development must be pursued simultaneously.

In the case of healthcare, it is a false dilemma to put problems of underdevelopment such as malnutrition, infections, and pathologies related to reproduction, against the important opportunities that emerge in biotechnology, information technologies, and telecommunications—which can translate into greater possibilities for the diagnosis, treatment, control, and prevention of common diseases. This means that the Mexican health system should continue to improve its programs by incorporating new cost-effective interventions, increasing coverage for services that are already nearly universal, strengthening primary healthcare programs, promoting community medicine, and developing a health culture based in education. Furthermore, the National Health System should have the means to identify, evaluate and, when necessary, implement the rapidly emerging technological innovations that can strengthen healthcare in a variety of ways.

These thoughts were included in the 2002 declaration at the World Health Organization stating that Mexico cannot afford to be indifferent and passive about genomic medicine. The potential benefits that genomic medicine offers are significant, and it is absolutely essential that these opportunities be considered as part of the national *health programs (Jiménez-Sánchez, 2003).*

At that time, it was clear in Mexico that genomic medicine will translate into a new paradigm for healthcare, with a number of opportunities that would represent important benefits for the Mexican population. In addition, the solid infrastructure in genetics and clinical medicine, along with the enthusiasm to develop genomic sciences in Mexico, represented significant assets that could serve as the basis to develop genomic medicine. Moreover, it was recognized that the development of genomic medicine would require the analysis of genetic variations in the Mexican population, as well as a robust human and technological infrastructure to support/facilitate research and implementation programs. Thus, genomic medicine clearly was not an "out of the box one-fits-all" solution.

The available evidence indicated the important benefits that genomic medicine could represent for Mexico, as well as the risks if such development was delayed. These included lack of access to novel knowledge and applications to public health, and the risk of increasing Mexico's dependence on developed economies in sensitive areas such as health. This led to the decision of incorporating genomic medicine as a part of Mexico's National Health Plan. As a result, it stimulated the development of cutting-edge infrastructure to implement world-class genomic medicine, oriented to the development of early interventions for prevention, diagnosis, and treatment of common diseases such as hypertension, type II diabetes mellitus, asthma, acute myocardial infarction, and a number infectious diseases that are becoming increasingly relevant in Mexico as part of the epidemiological transition in progress (Jiménez-Sánchez, 2003). The sustained development of this strategy would lead to improvement of healthcare in Mexico, and makes it reasonable to predict an important economic impact related to the reduction of health-related costs, mainly those of chronic treatment and loss of productivity from individuals with common diseases (Jiménez-Sánchez et al., 2002a).

A major component of this strategy was oriented toward educational programs aimed at professionals and the general public. The development of a national platform in genomic medicine will lead to the creation of infrastructure to develop training programs at different levels. In addition, such a strategy would lead to new opportunities to increase participation in a knowledge-based economy, including the stimulation of the genomic industry as a means to contribute to the economic development of Mexico (WHO, 2002). Although the costs of this initial infrastructure seemed high, they were relatively moderate compared with the financial costs that result from the burden of disease or the dependence on other countries with expertise in such a significant strategic area.

Mexico has extraordinary opportunities to identify genetic variants associated with medical traits, due to the availability of isolated populations, which are highly *inbred and genetically homogenous. We suggested that* international collaborations should be stimulated; however, abusive relationships must be avoided in which samples from Mexicans are taken to more industrialized countries, impeding access to research and results. This has occurred in the past in the field of archaeology and in the study of Mexican fauna and flora. For these reasons, it is strategically important that Mexico takes advantage

of the new knowledge and technologies generated by the HGP. To do this, it will be necessary to train a critical mass of researchers, professionals, and technicians who have the capacity to assimilate, develop, and apply genomics to medicine (Jiménez-Sánchez et al., 2008).

ANCESTRY OF THE MEXICAN POPULATION

Mexico is the fourteenth largest country in the world, with a total area of 1,972,550 km^2 and close to 112 million inhabitants (INEGI, 2005). Its varied topography results in a variety of climate conditions, from arid deserts in the north to rainy tropical climates in the south and along the southeast coast. In addition, geographically distant regions have different demographics. These differences arise from both the country's distinct ancestral components and from the demographic conditions that characterize each region (Gerhard, 1986). During the pre-Hispanic era, the majority of the population was concentrated in the center and south of Mexico. The ethnic groups that inhabited the north of Mexico did not have linguistic, religious, or political unity. It was not until two centuries after the Spanish conquest that the northern regions drew the attention of the Spaniards, mainly because of the silver deposits discovered in those regions (Gerhard, 1986). After the notable reduction of the Amerindian population as a consequence of epidemics between 1545 and 1548, African slaves were brought into Mexico. These slaves mixed both with indigenous inhabitants and with Mestizos, and many were transferred to other regions to work in mineral mines. The Yucatan Peninsula, located in the southeast region of Mexico, was populated by different Amerindian groups who were decimated by diseases, which reduced the original population by at least one-half (Gerhard, 1991). This unique history translates into a population that is derived from more than 60 groups of local Amerindians, Europeans, and, to a lesser degree, Africans. A survey of the language and geographic location of Amerindian groups in Mexico is currently being conducted. These groups have mixed throughout the past 500 years, leading to the Mestizo population that currently represents 80% of Mexicans (Gonzalez Burchard et al., 2005). Because of this unique demographic history, it is important to characterize the genetic composition of the Mexican population as an initial step toward the successful development of genomic medicine in Mexico.

STRATEGY TO ESTABLISH A NATIONAL INSTITUTE OF GENOMIC MEDICINE

As is the case for the majority of developing countries, Mexico faces demographic and epidemiological transitions that have important implications for the standards of disease, disability, and mortality. On one hand, it faces the unresolved problems of infections, malnutrition, and reproductive health, and on the other, the emerging challenges of chronic and degenerative diseases of the industrialized world. In Mexico, the adult population has a high prevalence of diabetes mellitus (7.0%), hypertension (30.8%), and obesity (29.4%; Olaiz, 2006). The two main causes of mortality are cardiovascular diseases (22.9%) and diabetes mellitus (15.3%; INEGI, 2005). Preventing these diseases is a key strategy to reducing their significant economic and health burden.

In 2000, an initial working group analyzed reasons why genomic medicine represented important opportunities for healthcare in Mexico. The group identified the following eight areas of opportunity: (1) contribution to a more individualized, predictive, and preventive medical practice; (2) strengthening of scientific research and technology in Mexico; (3) potential cost reduction of healthcare; (4) development of pharmacogenomics; (5) generation of novel products and services; (6) strengthening of the potential to participate in the knowledge economy; (7) timely development of an ethical and legal framework for genomic medicine in Mexico; and (8) the development of public education programs related to genomics and society.

The establishment of the National Institute of Genomic Medicine was preceded by multi-institutional efforts aimed at developing a national platform for genomic medicine in which this institution would have a central role. In 1999, the Mexican Health Foundation (FUNSALUD), then under the leadership of Dr. Guillermo Soberón, organized a working group composed of specialists from the NHIs and UNAM. The group analyzed the state of the art of genomic sciences at that time, as well as the possibilities to use such progress to improve healthcare for the Mexican population.

Simultaneously, the federal government of Mexico, then headed by President Ernesto Zedillo, began to generate the infrastructure that Mexico would need to coordinate public policies and actions regarding the human genome. In consequence, José Antonio González Fernández, Secretary of Health at that time, established the National Commission for the Human Genome on October 23, 2000. This organism was created by the action of an executive decision of the President of Mexico, which was co-signed by the secretaries of health and education. This Commission provided an ideal forum for discussion at the highest levels of decision making, and was instrumental in speeding the process of developing genomic medicine in Mexico.

In 2000, a strategic alliance was established to generate synergies for the project. This alliance was integrated by the Department of Health (SSA), UNAM, CONACYT, and FUNSALUD. Its goal was to evaluate the best way to create an institution that would coordinate the development of

a national platform of genomic medicine. On August 27, 2001, with the assistance of specialists from the McKinsey consulting firm, this group produced a feasibility study to launch the initial steps for a national platform of genomic medicine in Mexico. This study recommended the creation of a Consortium to promote and perform executive and detailed studies, in order to create and develop the first National Health Institute in Latin America dedicated to genomic medicine, while the Mexican Congress analyzed a bill to create the National Institute of Genomic Medicine (INMEGEN). As a result, the Consortium for the Institute of Genomic Medicine was established on November 22, 2001.

The Consortium was designed with a very specific goal, namely to promote and perform executive and detailed studies to establish and develop INMEGEN (Jiménez-Sánchez et al., 2002b). Its organic structure was headed by a governing board, integrated by Julio Frenk, Secretary of Health; Juan Ramon de la Fuente, Rector of UNAM; Jaime Parada Avila, Director of CONACYT; and Antonio Lopez de Silanes, President of the Board of Directors of FUNSALUD. From it, a board of directors was formed that included representatives from each of the institutions of the alliance: Misael Uribe (SSA), Alfonso Serrano Perez-Grovas (CONACYT), Juan Pedro Laclette (UNAM), and Guillermo Soberón (FUNSALUD), along with a fifth person, Dr. Jorge Rosenkranz, who was included because of his experience in the fields of research and the industrial sector. Guillermo Soberón was appointed coordinator of this board. Subsequently, they elected Gerardo Jiménez-Sánchez as director of the Consortium, and Cuauhtemoc Valdes from FUNSALUD was invited to take care of administrative coordination.

The Consortium existed from January 2002 until May 2005, when it had successfully achieved its goal. The director of the Consortium periodically presented the work programs and reports for the consideration of the board of directors. The board monitored and supervised the activities and financial status. Furthermore, the Board of Governors was kept informed on an ongoing basis, and periodic meetings were held to formally present the appropriate progress reports.

Given the novel nature of genomic medicine, the Consortium dedicated part of its efforts to broadly disseminate information on the nature and the scope of the project to the academic community and the general public. Throughout the project, more than 100 lectures were held. Many of them were offered at the most distinguished academic institutions, including El Colegio Nacional, the National Academy of Medicine, and the Industrial's Club, the latter aimed at the business community. These conferences were delivered both by domestic and foreign speakers such as Barton Childs, Francis Collins, Aravinda Chakravarti, David Valle, Rick Ward, Julio Frenk, Juliana Gonzalez, Gerardo Jiménez-Sánchez, and Guillermo Soberon. In addition, the first National Congress of Genomic Medicine was celebrated in 2004 with participation of top international academic leaders in genomic medicine.

Antonio López de Silanes, a prominent businessman in Mexico and, at that time, president of the Board of Directors from FUNSALUD, organized a group of 37 FUNSALUD associates with experience in the pharmaceutical industry, health, and insurance services, along with other people interested in the topic. This group made it possible for FUNSALUD to contribute to the trust of the Consortium. Additionally, some companies (Laboratorios Silanes, GlaxoSmithKline, Merck Sharp & Dohme, and Novartis) provided support for specific projects and actions of the Consortium. One example of such support was the establishment of the Silanes-INMEGEN Award in genomic medicine in 2002, and the Silanes-FUNSALUD Chair of Genomic Medicine in 2004.

Since then, FUNSALUD has been disseminating information about genomic medicine on its own, as well as through joint events with the National Academy of Medicine and through written reports published in the *Gaceta Medica de Mexico*. An edition of *Cuadernos FUNSALUD* was dedicated to reviewing the achievements of genomic medicine and the opportunities for the pharmaceutical industry.

As has been mentioned, the Consortium was in charge of formulating the distinct projects and documents that served as the basis for the discussion of this initiative with the legislators at that time, mainly with those in the health and science and technology committees from each of the two chambers of the Mexican Congress, as well as with the Department of the Treasury to lay the foundations of the financial feasibility of the project.

The Consortium produced a number of national congresses, seminars, and courses. Among those, Gerardo Jiménez-Sánchez designed three courses that integrated genomic medicine and clinical practice; namely, "introduction to genomic medicine," "pediatric applications of genomic medicine" and "genomic applications in internal medicine," which were registered with the Faculty of Medicine at UNAM. In addition, an electronic portal was established to identify potentially interested candidates to pursue a career in the field. This portal produced extraordinary results: an enormous interest was seen among young doctors, biologists, chemists, engineers, and other professionals, many of them Mexicans receiving graduate training abroad. Several of them subsequently joined INMEGEN.

The research activities soon began, and it became necessary to construct an adequate space for the laboratory work and for highly specialized technological units. We established the initial headquarters of the Consortium on a 3000m^2 area at the Zafiro corporate tower in south Mexico City. In this space, we established

the first laboratories and the following three core centers: sequencing, microarrays, and high-performance computing.

The results obtained by the Consortium were published in two separate reports (Jiménez-Sánchez, 2002, 2004b), which were approved by the Board of Governors and the Board of Directors of the Consortium. They were made publicly available and widely distributed to the institutions and public in Mexico.

THE FOUNDATION AND INITIAL DEVELOPMENT OF INMEGEN

In Mexico, the law of the National Institutes of Health indicates that NIHs are to be created by the Mexican Congress. The work done by the Consortium laid the foundations for discussion in the Mexican Congress regarding the need for the National Institute of Genomic Medicine. Thus, the process that began at the end of 1999 concluded in April 2004, following a significant number of actions to promote such legislation. On July 19 of the same year, a decree was published creating the National Institute of Genomic Medicine, in a ceremony headed by then President of Mexico, Vicente Fox, and in which then Secretary of Health, Julio Frenk, and the president of the Health Commission of the Chamber of Deputies, Jose Angel Cordoba Villalobos, participated. It is worth mentioning that Dr. Cordoba Villalobos followed Julio Frenk as Secretary of Health on December 1, 2006.

During the administration of President Felipe Calderon, INMEGEN received a visit from the First Lady of Mexico, Ms. Margarita Zavala, who inaugurated the first three High-Technology Core Units on the third anniversary of the founding of the institution. Later, on May 11, 2009, during the presentation of the results from the Mexican Genomic Diversity Project, the President of Mexico expressed his support of INMEGEN and urged it to continue working toward full development of genomic medicine in Mexico.

According to the Law of the National Institutes of Health, INMEGEN is the National Reference Center for matters related to the human genome and its medical applications. It has the following main objectives: (1) to perform clinical, epidemiological, experimental, technological, and basic studies and research in its areas of specialty for the understanding, prevention, diagnosis, and treatment of diseases and the rehabilitation of the ill; (2) to promote public health measures; and (3) to perform activities inherent to the National Institutes of Health, except for those related to providing medical services. The latter is relevant because in Mexico, all NIHs except for two (Public Health and Genomic Medicine) are highly specialized hospitals in addition to research institutions, whereas INMEGEN was planned as an institution where clinical research would be carried out using the clinical infrastructure of the rest of the NIHs. This feature, called the *horizontal dimension*, was designed during the feasibility study to develop robust synergies without diluting INMEGEN's research budget. In addition, the Institute was tasked with promoting projects to develop specialized technology based on specific projects involving technological innovation.

The same law defines the administrative bodies of the Institute. Thus, the Governing Board was established for the period from 2004–2009, in accordance with Chapter III (dedicated to the governing bodies), Article 14 of the cited law. From the first to the fifth years, the Governing Board consisted of the Secretary of Health, who presided over it; the General Coordinator of the National Institutes of Health; a representative of the Department of the Treasury; the President of the Board of Trustees of the Institute; a representative of the educational sector; and four invited members designated by the Secretary of Health from other institutions who were recognized for their moral quality, merits, prestige, and experience in their areas of expertise. These last members are invited for four years, with the possibility of being reappointed for one additional term; however, none of them were reappointed by the following federal administration. In addition, the Governing Board had a secretary and a deputy secretary.

During 2004, this Governing Board was presided over by the Secretary of Health, Dr. Julio Frenk Mora, and was composed of the following members: Dr. Jaime Sepulveda Amor, Deputy Chairman and General Coordinator the National Institutes of Health; Dr. Guillermo Soberon, President of the National Commission of Bioethics; Dr. Manuel H. Ruiz de Chavez, Executive President of the Mexican Health Foundation; Dr. Juliana Gonzalez Valenzuela, Emeritus Professor of the Department of Philosophy and Arts of UNAM; and Dr. Jorge Rosenkranz Weiner, distinguished Mexican scientist with special expertise in intellectual property in biotechnology; Mr. Sergio Montaño Fernandez, representative of the Department of Treasury, and Dr. Rene Santoveña Arredondo, representative of the educational sector and Rector of the Autonomous University of the State of Morelos; Mr. Carlos Eduardo Represas de Almeida, President of the Board of Trustees and Chair of the Governing Board of Nestlé Mexico, S.A. de C.V.; and Sergio Vazquez Cordova, as Commissary.

The members mentioned above formed the Governing Board until 2006. With the change of federal administration, beginning in 2007, Dr. Jose Angel Cordova Villalobos, Secretary of Health, presided over the organization, and Dr. Julio Sotelo Morales joined as Alternate Chairman and Trustee of the Coordinating Commission of the National Institutes of Health and High-Specialization Hospitals.

Several other members of the board changed, including the four invited members named.

In September 2008, given that no members were reappointed upon concluding their terms, the following new members joined: Adolfo Martinez Palomo, Emeritus Investigator of the Center for Research and Advanced Studies of the IPN; Dr. Ruben Lisker Yourkowitzky, Director of Research of the National Institute of Medical Sciences and Nutrition Salvador Zubiran; Dr. Misael Uribe Esquivel, Chief of the Department of Gastroenterology of the National Institute of Medical Sciences and Nutrition Salvador Zubiran; and Dr. Teresita Corona Vazquez, General Director of the National Institute of Neurology and Neurosurgery Manuel Velasco Suarez. Later, in July 2009, Dr. Jose Narro Robles, Rector of UNAM, was invited to represent the educational sector as a substitute for Dr. Fernando Bilbao.

It is worth mentioning that according to Article 16 of the cited law, this Governing Board had the following non-delegable duties conferred by the Federal Law of Public Enterprises: (1) approve the distribution of the definitive annual budget of the entity and the investment programming, according to the total amount authorized by its budget; (2) approve budget adjustments for its programs, which does not imply changes in total authorized amount, investment resources, projects financed by external credit, or in the fulfillment of the institutional objectives and goals; (3) establish guidelines for the application of self-generated resources; (4) authorize the use of spaces in the areas and facilities of the Institute that are not for hospital use; (5) approve and modify the basic structure of the institution according to the total budget authorized for personal services; (6) establish a system for continuing professional education for the personnel of the Institute; (7) determine the rules and the percentages of additional salary for the personnel who participate in extramurally- funded research projects, and the royalties that result from the application or exploitation of industrial and intellectual property rights that are derived from projects performed by the Institute; and (8) evaluate and approve candidates for executive posts presented by the General Director. In parallel, according to Article 17, the Governing Board of the Institute carried out ordinary sessions twice each year in addition to the extraordinary sessions proposed by its Chair (Jiménez-Sánchez, 2009).

Based upon the above, the Governing Board of INMEGEN chose Dr. Gerardo Jimenez-Sanchez as the founding General Director of the Institute. He had served as Director of the Consortium for the Institute of Genomic Medicine. In addition, the 2004–2009 Work Program for the National Institute of Genomic Medicine (Jiménez-Sánchez, 2004a) was prepared by Dr. Jiménez-Sánchez as part of the selection process for INMEGEN's General Director.

THE BOARD OF TRUSTEES

The Board of Trustees was established according to Article 21 of the Law of the National Institutes of Health. According to Article 23 of the Law, this board comprised a president, a secretary, a treasurer, and the members, all of whom were recognized for their reputations, were part of the social and private sector or of the community in general, and who had a dedication to service. The operations of the Board of Trustees and the tenure of its members in their posts were established by corresponding internal rules of operation. It is worth mentioning that the posts of the members were honorific, and they did not receive remuneration, emolument, or compensation, according to Article 24 of the law mentioned above.

The Board of Trustees of INMEGEN assisted the Governing Board and the General Director through the development of the following functions, according to Article 25 of the cited law: (1) support the activities of the Institutes and formulate suggestions aimed at improving performance; (2) contribute to the procurement of resources that promote the fulfillment of the objectives of the Institutes; and (3) complete other functions indicated by the Governing Board.

Within this legal framework, in the first ordinary session of the Governing Board celebrated on March 30, 2005, the integration of the Board of Trustees of INMEGEN was authorized, according to the current regulations; the Board of Trustees was included as an advisory and consulting body, which had the goal of supporting the work program of INMEGEN, mainly by encouraging excellence in scientific research, by training highly specialized human resources, and by facilitating the link with the business sector that will allow the medical applications derived from genomic medicine research to be translated into goods and services that contribute to the healthcare of Mexicans.

In this context, in August 2004, the Secretary of Health, Dr. Julio Frenk Mora, president of the Governing Board of INMEGEN, invited Mr. Carlos Eduardo Represas de Almeida to join and preside over the Board of Trustees and to join the Governing Board of INMEGEN as a member. Mr. Represas has distinguished himself as a leading member of the Mexican Health Foundation, having served as Vice President of Finance of that organization, and as a member of the Board of Directors on various occasions. His performance as chair of the Board of Trustees was of great value in directing the activities of the organization to consistently benefit the institution and improve its performance.

The Board of Trustees of the Institute was composed of distinguished members of the business sector, whose work was fundamental in the support of INMEGEN's program of work. This collegial body was composed of the following founding members: Carlos Eduardo Represas

de Almeida (Chair), Jorge Arevalo Chavez (Secretary), Emilio Azcarraga Jean, Luis German Carcoba García, Henry S. Davis, Pierre Froidevaux Chavan, Marcos Martinez Gavica, Ernesto Rubio del Cueto, Jaime Serra Puche, and Nina Zambrano.

This board contributed in a creative way to add value to the development of the activities of INMEGEN, through a work program related to the one proposed by the General Director and approved by the Governing Board (Jiménez-Sánchez, 2004a). The board established a trust fund to receive funds on behalf of INMEGEN, and also performed various activities aimed at supporting the development of the Institute. Among these, there was the creation of an informative video on INMEGEN and the establishment of strategic partnerships, for example with Nestlé, a company headquartered in Switzerland that develops scientific research of the highest level, including studies related to genomics and proteomics. This relationship led to the establishment of two scholarships and a Nestlé Chair of Nutrigenomics to promote the development of this field in Latin America.

ALIGNMENT WITH FEDERAL PROGRAMS

The creation and operation of INMEGEN contributed to the development of one of the areas of interest indicated by the National Health Program of 2001–2006 (PRONASA); the creation of INMEGEN was considered to be within the scope of the tenth strategy: "Strengthen investment in human resources, research and infrastructure in health." In particular, this project was related to the objectives stated in action line 10.4 of the National Health Program: "Strengthen the research and development of health technology."

Because of the federal goals stated above, it is important to mention that INMEGEN's 2004–2009 Work Program was in the context of the 2001–2006 National Health Program, as well as the Health Research Action Program. In this context, the creation of INMEGEN responded to the challenge of improving health research quantitatively and qualitatively. In particular, the strategy was intended to generate scientific innovation and to make the development of genomic medicine in Mexico a reality through a multidisciplinary approach and a focus on sectorial collaboration and inter-sector liaison. With the creation of INMEGEN, the national health system and its public institutions were strengthened by the promise of research in genomic medicine and training of human resources.

Furthermore, to contribute to the objectives of the 2007–2012 National Health Program, INMEGEN aligned its efforts with the following strategies: fortify and integrate actions that promote health and prevent diseases; promote investment in systems, information technologies, and communications that improve the efficiency and the integration of the sector; strengthen research and training in the healthcare field; and support the ability to offer health services through the development of the necessary infrastructure and equipment.

THE 2004–2009 WORK PROGRAM FOR INMEGEN

The Governing Board of INMEGEN approved the Work Program for the period of 2004–2009 that was proposed by Dr. Gerardo Jiménez-Sánchez as part of the selection process of the General Director of the Institute. In this program, the mission, vision, and objectives of INMEGEN were established, which included priorities for the initial development of the Institute and which were grouped into nine strategies.

The mission of INMEGEN is "to contribute to the healthcare of Mexicans by developing excellent scientific research and providing high-level training for human resources, which will lead to the medical applications of genomic knowledge through an innovative culture, cutting-edge technology, and strategic alliances that adhere to universal ethical principles."

The vision of the Institute is "to be the undisputed leader in Latin America and one of the main research hubs worldwide for developing genomic medicine, undertaking scientific research, training human resources, encouraging technological innovation, and developing goods and services. The most important values to INMEGEN are excellence, honesty, creativity, responsibility, institutional pride, loyalty, and respect."

The Work Program included nine specific strategies with 44 action lines and 125 goals to achieve during the first five years of INMEGEN's existence. The strategies were as follows: (1) organizational design: "the INMEGEN system"; (2) high-level scientific research in genomic medicine; (3) excellence of training and teaching in genomic medicine; (4) cutting-edge genomic technology applied to medicine; (5) establishment of the initial infrastructure; (6) development of strategic alliances for the integral development of genomic medicine; (7) translation of scientific knowledge into health goods and services; (8) compliance with the ethical, legal, and social frameworks of genomic medicine; and (9) administration of the research and teaching services.

Currently, INMEGEN (www.inmegen.gob.mx) is one of the twelve NIHs of Mexico. INMEGEN constitutes the cornerstone of the Mexican strategy to develop a national program in genomic medicine. The organization is designed to grow as an autonomous institution, linked to the educational and health sectors across the entire country. Its main funding source comes from federal fiscal funds, although it also receives support in the form of donations, both national and international. During its

first three years of operation, the Mexican government assigned more than 125 million dollars for its initial operations and infrastructure. This included modern facilities located in Mexico City that consisted of high-technology genomic units for sequencing, genotyping and expression analysis, supercomputers, proteomics, and biomarker discovery laboratories. In addition, a research center for the ethical, legal, and social implications of genomic medicine was established, along with a center for the incubation of businesses and technology transfer. Very soon, INMEGEN will open its new 60,000m^2 facilities on the NIHs campus, in the south of Mexico City (Figure 99-1).

The scientific agenda of INMEGEN includes the understanding of the genomic structure of the Mexican population and the study of its most complex health problems, which include diabetes, obesity, cardiovascular diseases, infections, autoimmune diseases, macular degeneration associated with age, and tumors of the thyroid, breast, prostate, and blood. The majority of the projects involve the identification of genes associated with common disease risk and the biomarkers for their early diagnosis and prognosis. Furthermore, pharmacogenomics is an important part of the scientific agenda, given that strategies are being proposed to create more effective and less toxic medicines for the Mexican population (Seguin et al., 2007).

MAIN ACHIEVEMENTS OF INMEGEN DURING 2004–2009

During its first five years of operation, INMEGEN laid the foundation necessary to develop a national platform for genomic medicine in Mexico. The institute recruited a group of talented professionals who were dedicated to the construction of an innovative institution, and who shared an ambitious vision for the future. This vision was one of developing genomic medicine oriented to ease national health problems in the context of the programs established by the federal government.

The organizational design of INMEGEN was the product of careful planning aimed at developing a modern institution whose contributions would not only have a direct impact on public health, but would also be governed by ethical guidelines that guarantee adherence to universal ethical principles. Thus, the Institute established its Code of Ethics and Conduct, in addition to 34 internal normative manuals and instruments, which were incorporated into the daily activities of the personnel through more than ten seminars about organizational culture.

The main research areas considered in INMEGEN's 2004–2009 Work Program were population genetics, metabolic diseases (obesity and diabetes mellitus), cardiovascular diseases, cancer, infectious diseases, and pharmacogenomics. Over time, scientific progress generated the opportunity to broaden these areas of research. So, beginning in 2007, new areas of research were added, including medical proteomics, functional genomics for cancer, nutrigenomics, and genomic eye diseases. Currently, INMEGEN carries out genome-wide association studies (GWAS) on age-related macular degeneration, obesity, systemic lupus erythematosus, and cardiovascular diseases. INMEGEN also analyzes the expression of leukemias, sarcomas, and breast (Hidalgo-Miranda & Jiménez-Sánchez, 2009), lung, thyroid, and prostate cancers both in humans and in experimental mouse models

Figure 99-1 The National Institute of Genomic Medicine in Mexico City. Located in the Campus of the National Institutes of Health.

(Mendoza-Villanueva et al, 2008). In the area of medical proteomics, INMEGEN is working to discover biomarkers for melanoma, lung, and breast cancer through an analysis of the proteomic profiles of blood, saliva, and other body fluids.

ACADEMIC ACTIVITIES AND TECHNOLOGICAL INFRASTRUCTURE

The selection and recruitment process for the academic personnel of INMEGEN ensures that each member of the team can contribute to specific areas of medical genomics. By August of 2009, INMEGEN had recruited 31 researchers organized in nine laboratories, each of them with cutting-edge technology. They conducted 42 scientific research projects (Table 99-1), 11 of which received external financing. The results included over 55 peer-reviewed publications, training of human resources, and the first two National Congresses of Genomic Medicine in Latin America. In addition, a laboratory of genomic diagnosis was established to develop genomic services, initially those related to pharmacogenomics of oral anticoagulants (Acenocoumarol and Warfarin) and the antiretroviral Abacavir.

TABLE 99-1 SELECTION OF RESEARCH PROJECTS DEVELOPED AT INMEGEN, 2004–2009.

1. Genomic diversity of Mexican populations.
2. GWAS study for essential hypertension in the Mexican population.
3. Genomic structure of the angiotensinogen gene.
4. Genomic variability associated with age-related macular degeneration.
5. Analysis of proteomic profiles in the saliva of smokers with lung adenocarcinoma.
6. Resequencing analysis of genes related to drug metabolism.
7. Pharmacogenomics of Acenocoumarol and Warfarin.
8. Pharmacogenomics of Abacavir.
9. Analysis of maternal and paternal lineages with mitochondrial markers and of the Y-chromosome in the Mestizo population.
10. Genomic risk analysis of morbid obesity in the Mexican population.
11. The regulatory role of *CEMP1* during the process of in vitro cementogenesis/osteogenesis.
12. Identification of early biomarkers for diabetic nephropathy.
13. Genomic basis of autoimmune diseases among the Mexican population.
14. Identification of polymorphisms among genes associated with asthma.
15. Genetic risk factors for obesity and metabolic syndrome.
16. Allelic variants associated with the oxidative stress response in health and disease.
17. Genetic association with susceptibility to asthma and treatment response.
18. The Nrf2-Keap1 signaling pathway in the susceptibility to myeloid leukemia.
19. Early molecular biomarkers of liver cancer.
20. Global expression analysis in a three-dimensional culture model in different types of tumors.
21. Regulation of the expression of Smac/DIABLO.
22. Sequence analysis of the amyloidogenesis of immunoglobulin light chains.
23. Proteomic biomarkers associated with melanoma.
24. Proteomic analysis of breast cancer and identification of cancer biomarkers.
25. Proteomic profiling in gastric cancer.
26. Ethical, legal, and social implications of genomic medicine.
27. Pan-American Initiative in Bioethics.

The high-technology units established at INMEGEN focused on supporting specific research and teaching programs of the Institute and other affiliated institutions. These units included the genomic sequencing and polymorphism analysis unit, powered by Affymetrix, Illumina, and Applied BioSystems platforms, the genomic expression unit, the medical proteomics and biomarker identification unit, and the validation area, which has the capacity to use tissue arrays for the simultaneous and comparative analysis of proteins. All of these units have access to the most advanced technology in genomic medicine.

The high-technology units were connected to a supercomputer and an information technology system, which had a capacity of over 2.2 million operations per second. This was done for the purpose of meeting the analysis requirements of the research projects. Additionally, a storage capacity of 22 terabytes was implemented, which was essential for storing the large quantity of genomic data generated by the various research projects. This infrastructure included computer and telecommunication networks to support the projects of both local scientists and others located in various institutions around the world.

Training of human resources increased rapidly, as various courses were formally integrated into undergraduate and graduate programs. Over 20 courses were offered during this period, attended by 455 students from across the country. Furthermore, more than 42 graduate students from various institutions of higher education carried out their scientific research projects in the laboratories of INMEGEN, obtaining their respective degrees.

INMEGEN hosted more than 130 academic events of the highest level and has been honored with the participation of distinguished international speakers. These events included the first and second National Congresses of Genomic Medicine. The participation of the medical, academic, and scientific community of Mexico and other parts of the world was overwhelming, with more than 20,700 individuals participating.

The initial facilities of INMEGEN included a Center for Information and Documentation (CID), which specialized in the different areas of genomic medicine. The CID collection contains more than 1100 books and subscriptions to 167 specialized scientific journals. Moreover, the innovative culture of the Institute led to the establishment of an electronic system to provide more than ten different electronic services to both the personnel of INMEGEN and interested parties in other geographic locations.

Since its creation, one of the priorities of INMEGEN has been the development of scientific, academic, and business interactions with various organizations in Mexico and abroad. During 2005–2009, 48 cooperation agreements were signed (Jiménez-Sánchez, 2009). Such agreements have contributed to the development of a national platform of genomic medicine, thus creating synergies that will assure permanent world-class competitiveness.

The strengthening of the links with the academic sector continued in 2006, through academic and scientific collaboration with the University of Guanajuato, the Autonomous University of Tamaulipas, the Autonomous University of the State of Morelos, the National Council of Science and Technology, and the College of Postgraduates. In 2007, INMEGEN's interaction with the Institute of Anthropological Research of UNAM led to the project, "Lineages of mitochondrial DNA and of the chromosome in the Mestizo and indigenous Mexican population."

Important alliances were established with the departments of health in various states of Mexico, an activity that began at the end of 2004 through an interaction with the state of Zacatecas, which established a program for visits and rotations for students. Another collaboration with the state of Yucatan led to a pilot project to study cardiovascular diseases in the Mestizo-Mayan population.

In 2005 and 2006, collaboration agreements were formalized with the states of Yucatan, Veracruz, Sonora, Guerrero, Zacatecas, Guanajuato, and Tamaulipas. These states participated in the project to develop a genomic map of Mexican populations. They also stimulated information exchange related to scientific progress in genomic medicine, academic activities, technological services, and publications, as well as training of human resources and development of research projects.

The link with the industrial sector became an ideal space to explore nutrigenomics, one of the areas with the greatest potential in the coming years. During the second semester of 2006, INMEGEN's interaction with Nestlé, S.A. de C.V. began. The following year, the relationship was formalized with the signing of a collaboration agreement for the establishment of the "Nestlé Chair of Nutrigenomics" and the "Nestlé Fellowships in Nutrigenomics." The purpose of these positions was to support scientific research and training of human resources in nutrigenomics at INMEGEN. The positions also served to foster new ideas that could contribute to improve healthcare of the Mexican population.

The inauguration of the Nestlé Chair in Nutrigenomics was planned for a period of three years, with the goal of recruiting a senior researcher capable of conducting research on fundamental topics related to improving the health status of Mexicans through nutrition and genomics. Furthermore, two masters, doctoral, or postdoctoral positions were created under the name, "Nestlé Fellowship in Nutrigenomics." These positions were designed to encourage young Mexicans to develop proficiency in the area of nutrigenomics.

The selection process for the awardees of those fellowships began with the publication of a call for applications in the last quarter of 2007; three applications for study in nutrigenomics and two applications for the position of Chair of Nutrigenomics were received. By 2008, a review process was established by an ad-hoc group. Currently, Dr. Elizabeth Tejero holds the Chair in nutrigenomics.

The links with foreign institutions were of great importance, and the first contacts with organizations outside of Mexico began in 2004. These international organizations included the National Institutes of Health of France (INSERM), the National Institutes of Health in the United States, Johns Hopkins University, and the Broad Institute of Harvard University and the Massachusetts Institute of Technology. Vanderbilt University had an important role in developing collaborative efforts in the areas of ethical, legal, and social implications of genomic medicine, as well as in the areas of bioinformatics and pharmacogenomics.

In 2005, strategic alliances were established with the Translational Genomics Research Institute (TGen), under the direction of Dr. Jeff Trent, which turned into specific projects of academic and scientific collaboration. Furthermore, beginning on December 20, 2005, INMEGEN joined the "Public Population Projects in Genomics" (P3G) under the leadership of Professor Bartha Knoppers, a nonprofit international consortium with the main objective of promoting collaboration among researchers in population genomics through the creation of a public, open, accessible and transparent database.

In 2006, a collaborative agreement was established with the Interdisciplinary Center on Bioethics of the Pan-American Health Organization/World Health Organization for the purpose of training human resources, developing collaborative research projects on ethical aspects of genomic medicine, and exchange of information. Several publications resulted from this effort, particularly in the area of ethical, legal, and social aspects of genomic medicine.

In 2007, an academic and scientific collaboration agreement was signed with the Genome Institute of Singapore, represented by Dr. Edison T. Liu, Executive Director of the Institute. The purpose of this agreement was to strengthen and broaden cooperation efforts to establish research programs and other collaborative projects. Through this link, both institutions developed research activities in genomics, pharmacogenomics, educational opportunities, and ethical, legal, and social matters related to genomic medicine.

During the same year, INMEGEN's international collaborations were particularly productive. A collaboration with the United Nations University of Biotechnology for Latin America and the Caribbean was established. This agreement included the granting of funds to INMEGEN for the design and delivery of the course "Ethical, Legal

and Social Matters in Genomic Medicine," which was the first of its kind in Latin America. Similarly, as a result of the agreement between the *Centre de Recherche en Droit Public* of the University of Montreal and INMEGEN, the HumGen Spanish portal (http://www.humgen.umontreal.ca/int/partenaires.cfm?&lang=3) was launched. This portal serves as a Spanish-language tool to explore the ethical, legal, and social aspects of genomic medicine. It could also serve as a communication bridge between Canada and Latin America on legal and social matters related to genomic medicine.

In addition, INMEGEN organized an "International Meeting of Leaders in Genomic Medicine: Emerging Regulatory Aspects" in collaboration with the Drug Information Association (DIA). The event had attendees and speakers from Mexico, Latin America, the United States, Canada, Switzerland, India, Singapore, Belgium, and Japan, among other countries.

INMEGEN created a Center for Research on the Ethical, Legal, and Social Aspects of Genomic Medicine, which brought together researchers from different institutions who together developed scientific studies on new topics in this field. The Intellectual Property Program was also developed, and a business incubator called ProGen was established (http://progen.inmegen.gob.mx). The work of ProGen was tightly linked to INMEGEN research projects and also included matters of copyright, associated with multiple brands and characters in comic books elaborated by INMEGEN.

The National Institute of Genomic Medicine has played a fundamental role in the dissemination of information about genomic medicine, and it has also earned national and international recognition. The methods used to disseminate information turned out to be very effective. Among them, the design of three widely distributed comics on genomic medicine stand out, as well as the design of a bilingual web portal that has become a key site to spread genomic medicine information. Over 53 million successful consultations were made through INMEGEN's portal between 2004 and 2009, and more than 45 million documents were downloaded by users from 140 countries.

In addition to INMEGEN's initial facilities, the construction of its permanent headquarters is now 80% complete (Figure 99-1). This new facility will provide a 17-fold increase in space and technological capacities that will be essential for the next phase of Mexico's construction of a national platform of genomic medicine (Hardy et al., 2008).

The results from INMEGEN's first administration were released to the public in 2009 in a four-volume report entitled: "Report on the 2004–2009 Activities of the National Institute of Genomic Medicine" (Jiménez-Sánchez, 2009). This documents reports the full implementation of INMEGEN's Work Program and was approved by the Governing Board of the Institute (Jiménez-Sánchez, 2004a).

THE MEXICAN GENOME DIVERSITY PROJECT

The characterization of the genetic structure in the Mexican population was one of the strategic areas of research at INMEGEN. Such information will be an essential tool for the development of genomic medicine for the Mexican population. The development of this line of research is of special relevance in the context of the initial phases of the International HapMap Project, which did not include any Latin American populations (HapMap, 2005).

Mexican Mestizos constitute a recently admixed population, mostly composed of European, Amerindian, and African lineages. The genetic heterogeneity of Mexicans is derived from a range of different demographic dynamics in geographically distinct regions. The first stage of the project included the genotyping of 110,356 SNPs from 300 unrelated individuals who identified themselves as Mestizos and originated from six geographically distant regions of Mexico (Silva-Zolezzi et al., 2009). Next, the genetic diversity, the patterns of linkage disequilibrium (LD), and the extent of common haplotypes were determined using data from these individuals along with information from the HapMap. The initial results of the project indicated that, even when there are regional genetic differences among Mexican subpopulations, these groups are sufficiently similar to be analyzed as one single group. However, the results of this study provided evidence of the population structure of Mexicans that should be considered when designing and analyzing genomic association to human disease. The initial analysis used a set of 2824 informative markers for ancestry derived from three populations of the HapMap. The analysis indicated that there are different proportions of mixes among Mestizos, and it showed a fourth ancestral component that is present in different proportions and that correspond to the Amerindian contribution (Silva-Zolezzi et al., 2009). The results of this project indicate that a haplotype map of Mexican Mestizos would improve the selection of tag-SNPs and make it possible to better capture common genetic variations in studies on the associations of diseases common among the Mexican population. This is the first genome-wide genotyping effort of a recently admixed Latin American population that is available to the general public (http://diversity.inmegen.gob.mx).

To generate a more comprehensive description of the common genetic variations and to adequately describe the genomic structure of these populations, the SNP density will be increased to approximately 1.5 million. In addition, the ensuing analysis will include Amerindian populations. The results derived from these efforts will provide the foundation for translating knowledge of the genetic structure of the Mexican population into a better understanding of common complex diseases. Additional studies on the genomic structure will include the systematic

analysis of copy-number variations in the Mestizo and Amerindian populations.

The initial results of this project suggest that the genetic differences among Mestizos of various regions of Mexico are mainly due to differences in the ancestral contributions of European and Amerindian populations. Comparative analysis of the proportion of these contributions among the participating states demonstrated important differences among some of them. In the majority of the analysis, the samples of the central regions had a higher similarity to indigenous groups, while the samples from the northern regions were more similar to European populations. These findings are supported by the current and historical Amerindian population densities in these regions (Silva-Zolezzi et al., 2009).

An analysis of the shared alleles and haplotypes was performed to evaluate the degree of genetic variability that is shared among samples of Mexican Mestizos and the populations of the international HapMap project (Europeans, Africans, Chinese, and Japanese). The results indicated that Mexicans share 64% of the common haplotypes (present in more than 5% of the samples) with Africans, 75% with the population of Asia, and 80% with the populations of northern Europe. When the information is combined with the four populations from HapMap, the percentage of shared haplotypes rose to 96%. These results indicate that there is a percentage of genetic variability present only among Mexicans, and that this variability is derived from the Amerindian component of the Mestizo population. On the other hand, the results of the comparison among Mestizo populations indicate that a specific haplotype map for them would allow a better selection and would reduce the number of genetic markers necessary for association studies of complex diseases, making these studies more efficient and less expensive.

The analysis of private alleles was performed for the purpose of identifying genetic variants exclusive to Mexican populations that had a frequency greater than 5%, and that were absent from the populations examined in the initial phases of the HapMap Project (African, European, and Asian). Eighty-nine markers were identified, only in some of the Mexican populations analyzed. In addition, 86 of these markers were also found in the samples of the Zapoteca population, which indicates their Amerindian origin (Silva-Zolezzi et al., 2009).

The initial results of the project demonstrated the feasibility of generating a public genomic database of the Mexican population and a catalog of the most common variants (http://diversity.inmegen.gob.mx). This public resource will become an important source of information for the design of genomic studies aimed at finding genes associated with common diseases, not only in Mexico but also in many parts of Latin America.

The Mexican Genome Diversity Project does not include direct medical applications, but rather was designed as a public tool that will lay the foundation for clinical studies on genomic medicine that will be performed by researchers across the country and in other parts of the world. In addition, it will allow new areas of research to be explored that will help identify genetic variations associated with a predisposition to common diseases, and how individuals with those genes respond to medications. This project was funded with public resources assigned to INMEGEN, and developed with important donations from the Mexican Health Foundation and the Gonzalo Rio Arronte Foundation.

The Mexican Genome Diversity Project has represented important progress for genomic sciences in Mexico. In addition, it has stimulated the recruitment of a critical mass of researchers in various disciplines. Furthermore, the technological infrastructure created by this project has become a valuable asset. These accomplished milestones, combined with our highly qualified scientists and the strategic liaisons established by INMEGEN, will contribute to develop a robust national platform in genomic medicine.

CURRENT AND FUTURE CHALLENGES

Mexico has invested significant efforts and resources to develop genomic medicine as a means to improve healthcare for the Mexican population. The results obtained in the first ten years of work have exceeded anyone's expectations in establishing the foundations of a mid-term national project.

Developing genomic medicine in Mexico to the point where it can perform at a leadership level and truly improve the healthcare of the Mexican population requires more than just solid scientific work. This ambitious goal will demand several cultural changes, including serious team efforts from medical clinics and scholars of the basic sciences, and a focus on common objectives. These collaborative efforts will be needed to address national health problems such as diabetes mellitus or breast cancer. It is likely that disarticulated projects will not be as successful with problems of this magnitude. It is important, therefore, that the Mexican model fosters a real component of innovation. In general, it will be the younger generations that will better deal with these challenges.

There are other challenges, including the need for new financing mechanisms, new incentives to innovate, and new ways to register intellectual property. The current model dominating scientific research has a significant impact on the scientists' income and creates a legitimate urgency to publish results. Although it has been proven that such systems increase the number and quality of scientific publications, they do not stimulate innovation in areas in which the risk of failure is significantly greater. In those areas, results are usually published after registration of the intellectual property. In recent years, the Mexican government has established programs to stimulate innovation

and to generate new business models based on scientific knowledge. These programs, located within CONACYT, reflect the awareness within the federal government of the strategic importance of innovation for economic growth. INMEGEN has established a synergy with CONACYT and the Mexican Institute of Industrial Property (www.impi.org.mx). The goal of this synergy is to develop mechanisms to incorporate innovation as a part of the local community, particularly in genomic medicine. Although there may be a number of genomic projects that will be developed by Mexican scientists alone, many genomic projects are generally the result of international collaborations, whereby Mexican scientists send samples to countries that have a more solid infrastructure. The goal of this collaboration is to combine forces and accelerate their research (Table 99-2A & 99-2B).

Even though international collaboration is desirable and encouraged, as the Mexican groups increase their critical scientific and technological mass, the collaborations tend toward a more equitable level of contribution, and groups are increasingly embarking on more independent research. Even though training programs in genomic medicine are recent, the number of applicants has significantly increased from dozens to hundreds at INMEGEN and the LCG. This clearly indicates that there is an opportunity to host new training programs in genomic sciences that respond to the needs of the current generations and contribute to the development of genomic medicine in Mexico. Unfortunately, "brain drain" continues to be a significant problem, mainly because of the lack of competitive salaries, the appropriate infrastructure, and funding opportunities for research throughout the country. The challenge of genomic medicine includes the recruitment and repatriation of qualified professionals, and the development of means to retain them for long enough to successfully develop their scientific contributions. In recent years, this situation has improved thanks to better infrastructure and consistent research programs that attract young researchers and bring them back to Mexico. CONACYT is facing this challenge by implementing a repatriation program, and a program aimed at retaining young scientists in Mexico. As a result, between 2001 and 2005, a total of 845 scientists were repatriated, some of which joined our genomic medicine program.

The limitations of sustained funding represent a challenge for science worldwide. Mexico's investment in research and development (R&D) is the lowest among member states of the Organization for Economic Cooperation and Development (OECD) and is equivalent to approximately a seventh of the average funding level of a member state of the OECD. It is significantly lower

TABLE 99-2A COLLABORATIVE AGREEMENTS SIGNED WITH INTERNATIONAL INSTITUTIONS 2004-2009

1. Translational Research Institute, Phoenix, AZ, USA
2. Bioethics Unit of the Pan American Health Organization – WHO.
3. Vanderbilt University, USA
4. McGill University, Genome Quebec, Canada
5. The State University of New York (SUNY), USA
6. United Nations University, UN
7. Genome Institute of Singapore, Singapore
8. Alcon Laboratories, USA
9. Centre de Recherche en Droit Public, Université de Montreal, Canada
10. Drug Information Association (DIA) USA
11. Foundation for the Popularization of Science and Technology and Institute of Science and Technology, Salamanca University, Spain

TABLE 99-2B COLLABORATIVE AGREEMENTS SIGNED WITH INSTITUTIONS FROM MEXICO 2004-2009

1. Yucatan Health Services; Autonomous University of Yucatan and FUNSALUD "Peninsular Chapter."
2. Zacatecas Health Services and Autonomous University of Zacatecas.
3. National Council of Science and Technology, MUO.
4. Sonora Health Services, the Autonomous University of Sonora and FUNSALUD.
5. Veracruz State Government and Veracruz University.
6. Ministry of Health of the State of Guerrero and Autonomous University of Guerrero.
7. National Institute of Public Health.
8. The State's Employees Social Security and Social Services Institute (ISSSTE).
9. National Institute of Public Health, Specific Agreement.
10. Guanajuato Health Services and Autonomous University of Guanajuato State.
11. Autonomous University of Morelos State.
12. Mexican Association of Human Genetics, MUO.
13. Mexican Association of Human Genetics, Specific Agreement.
14. Mexican Institute of Industrial Property.
15. "Gonzalo Río Arronte" Foundation.
16. Mexican Health Foundation, MUO.
17. Post-Graduate College (Agricultural sciences).
18. National Council of Science and Technology, HR Specific Agreement.
19. Tamaulipas Health Services and Autonomous University of Tamaulipas.
20. National Commission on Social Health Protection.
21. NESTLÉ, Mexico, MUO.
22. Ministry of Health of the State of Oaxaca; Autonomous University of Oaxaca "Benito Juárez" and Southeast Regional University.
23. Ministry of Health, Health Services of the State of Durango and State University of Durango.
24. Institute of Ophthalmology Conde de Valenciana Foundation.
25. Ministry of Health of the State of Campeche and Autonomous University of Campeche.
26. PROA Group Laboratories.
27. Federal District Government.
28. National Institute of Psychiatry "Ramón de la Fuente Muñiz."
29. National Autonomous University of Mexico.
30. Mexican Foundation for Promoting Education for Timely Prevention of Breast Cancer.
31. Genomi-k Laboratories.
32. Institute for Anthropological Research.
33. University Teaching and Research (Tec Milenio University).
34. Children's Interactive Museum (Papalote).
35. Hospital Juarez of Mexico.
36. Medix Products.
37. Nestlé México S.A.

than that of other emerging economies, such as China (0.7%), India (0.8%), or Brazil (>0.8%; OECD, 2006; Hardy et al., 2008). For comparison with other countries in Latin America, in 2004, Mexico invested 0.41% of its GDP in R&D, while Argentina invested 0.44%, Chile invested 0.68% and Brazil invested 0.91%. This represents a significant challenge for the successful development of a nascent field such as genomic medicine in Mexico. The Mexican government has not yet committed itself to investing in this promising field, but it is essential that the R&D situation be improved among public institutions in Mexico and that the technological infrastructure be kept updated. To reduce reliance on the federal government, various initiatives have been explored that provide additional support for genomic medicine. These include competition for international funding opportunities and increased private sector participation in R&D. Currently, around 35% of the spending on science and technology research in Mexico comes from the industrial sector (OECD, 2006). Even though this percentage is one of the lowest among member countries of the OECD, strategic alliances are being established between the industrial sector and public research institutions for specific projects, including those related to genomic medicine.

There are other challenges that play an important role in the successful development of genomic medicine. Some of these challenges involve the importation of equipment and chemical reagents from other countries. This is particularly important for the generation of new genomic technologies, because acquiring them involves significant costs from customs duties and tariffs, which must be paid for by the research budget. In addition, the excessive regulations and lengthy customs procedures damage many pieces of equipment and cause unfortunate delays during research projects.

As genomic medicine develops in Mexico, the need for modern legislation addressing both the ethical and social implications of genomic medicine will also increase. Questions of discrimination, confidentiality, equality in access to medical services, and financial and labor implications, among others, will require regulations based on Mexican laws.

We have learned valuable lessons during the planning and implementation of this strategy (Seguin et al., 2008). Some of them may be useful for similar emerging economies interested in developing genomic medicine. Careful planning is needed, along with the participation of the main organizations in the fields of health and education. Scientific and philanthropic organizations must work together on an equal level, which requires solid leadership at the highest levels to coordinate all of the efforts. It is important to determine the degree of academic, scientific, financial, and political capacity available before trying to establish feasible goals. It is also useful to take advantage of the local experiences of the past cases of both success and failure to design a more effective effort, to focus on ambitious but realistic goals, and to define specific challenges. These goals should include the development of programs for training, the development of infrastructure, and the selection of alliances. In addition, it is desirable that scientific research includes a component to translate knowledge into products and services, so that the programs are more attractive for public–private investment and contribute to the knowledge economy. Despite the large number of challenges ahead, Mexico has successfully begun to develop an expertise in genomic medicine. There is still much to do, but by carefully planning the commitments of the different actors in Mexican society, and by forming solid alliances, genomic medicine in Mexico will flourish and benefit the population through improved healthcare. Additionally, the country's scientific work, infrastructure, and commitment to innovation will have an effect throughout Latin America and will allow Mexico to participate in the worldwide transition toward a knowledge-based economy.

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