Bridging the genomics gap: the role of large-scale genotyping projects in the developing world and the importance of genomic sovereignty

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Sciences
University of Toronto

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Abstract

In recent years, there have been several proposals for large-scale human genotyping projects in the developing world. The dissertation presented here explores the motivations, opportunities and challenges of initiating locally led, large-scale genotyping projects documenting human genomic variation in the developing world. I analyze two case studies: the Indian Genome Variation Consortium in India and the University of Cape Town, Department of Human Genetics and the African Genomics Education Initiative in South Africa. These case studies, together with similar projects in Mexico and Thailand provide compelling reasons for pursuing these projects: the potential to address local health needs and reduce health care costs; the opportunity to stimulate economic development through investments in genomic sciences, and the availability of unique population resources. In an effort to capture the value of these investments and promote an equal stake in international collaborations, Mexico and India have developed guidelines and laws to protect local human genetic material as a sovereign resource, referred to here as ‘genomic
sovereignty’. Critics have suggested that it can impede international collaborations and reduce access to external funding. I provide an in depth analysis of genomic sovereignty and how it may contribute to each country’s aim of achieving health equity through investments in genomics, its relation to heritage and patrimony, and its potential limitations. The debate is critical, as the knowledge generated from large-scale human genomic research will need to be interpreted in larger international collaborative efforts before it can lead to health benefits. Qualitative case study methodology is employed and the primary data source consists of interviews conducted with key informants. The research described here provides a source of empirical description and analysis that is informing the framing of policies, principles and practices on how research infrastructure and capacity are being established for human genomic sciences in developing countries.
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Chapter 1
Introduction

1

1.1 Introduction

Genomics and associated genome-based technologies, such as genotyping\(^\text{i}\), have, in recent decades, been viewed as tools for improving health and lessening the burden of disease globally. Indeed, countries such as Canada, the United Kingdom and Japan have established large-scale genotyping projects in their populations as part of larger human genome epidemiology programs (e.g. the UK Biobank and Cartagene). Several publications however, have expressed concerns that developing countries\(^\text{ii}\) may not benefit from these advances\(^3\)\(^4\). Some have also made recommendations that measures be taken to strengthen research and capacity\(^5\). In 2002, a report released by the World Health Organization (WHO) *Genomics and World Health*, outlined many of the issues that needed to be addressed to ensure that all nations, including those in the developing world, would benefit from genomics and associated genome-based technologies. In the executive summary, the authors urged developing countries “to strengthen existing, or establish new centers and institutions engaged in genomics research with a view to *strengthening national capacity* and accelerating application of the advances in genomics relevant to countries’ health problems”\(^6\). The summary further suggested that, despite the high costs associated with the initial development and implementation of genomics and

\(^{i}\) An individual’s genotype is their genetic profile; the expression of which “contributes to the individual’s observable traits, called the phenotype”\(^1\). Genotyping assays an individual’s genotype. In large-scale genotyping projects, multiple genotypes are assayed and when cross-compared it can describe genotypic variation across the individuals sampled.

\(^{ii}\) Developing countries are defined here according to the World Bank Atlas grouping of low- and middle-income countries\(^2\).
genome-based technologies, the resulting cost efficiencies to a country’s health care system would be considerable, especially given the double burden of infectious and chronic disease and the expected predictive and preventative nature of genomic medicine. They advised that developing countries should leverage North-South and South-South collaborations, as well as regional networking opportunities in an effort to access these expected benefits. Otherwise, wrote the authors, the gap in the quality of health care between developing and developed nations would continue to widen.

It has also been implied by some that developing countries do not stand to benefit from genomics and genomic-based technologies because of the challenges associated with their cost, as well as the lack of capacity and infrastructure. Market segmentation trends for example, may result in unaffordable diagnostics, therapeutics and pharmacogenomics-based products with limited accessibility thereby increasing global health disparities. These critics have thus suggested that developing countries would be better served by focusing their limited resources on more immediate concerns, such as poverty, access to medicines, and clean water. Drug development however, has traditionally occurred in Western populations with little concern on how drugs can be used or accessed globally. As such, it is imperative that developing countries understand how their populations respond to disease and therapeutics if they are to avoid further increases in health disparities. Moreover, Daar and Singer (2005) and Séguin and colleagues (2007) have argued that developing countries can least afford to waste precious resources on ineffective diagnostics and therapies. Thus, it is more than likely that genomic and genomic-based technologies will be relevant to the health of people in developing countries.

While there has been much debate for why developing countries should invest in genomics, there have been few empirical analyses describing why and how these countries are doing so.
As of 2003, several locally led large-scale genotyping projects were proposed in India, South Africa\textsuperscript{iii}, Mexico, and Thailand to document human genomic diversity in their respective populations\textsuperscript{13,14}. The Indian Genome Variation (IGV) consortium and the Mexican National Institute of Genomic Medicine (INMEGEN) have since generated baseline information on single nucleotide polymorphisms (SNPs) and in some cases, copy number variation (CNVs) within local populations. These data may prove relevant to drug response or disease predisposition at the population level\textsuperscript{15,16}. Since being proposed, these large-scale genotyping projects have also established local scientific capacity in human genomics, through investments in training and infrastructure and stimulated modest growth and investment within the local private sector. In the long term, these initial investments may be used to conduct large-scale genomic epidemiology research (e.g. disease specific prospective studies) that will contribute to revealing the correlation between phenotypic variation, genotypic variation and the environment; ultimately improving their understanding of disease predisposition and drug response within their respective populations. It is widely believed that through such subsequent research (i.e. genomic epidemiology research programs), these developing countries will be capable of adopting and delivering genomic medicine\textsuperscript{iv}, a more cost-efficient method of treatment compared with the currently practiced trial-and-error method of diagnosis and treatment; effectively bridging the genomic divide\textsuperscript{4,18-27}.

\textsuperscript{iii} The project in South Africa was proposed in the early 2000s. In the face of several challenges (i.e. lack of political will and lack of funding) the South Africa project did not proceed, however I took to the opportunity to speak to those involved and scope out existing activity.

\textsuperscript{iv} Genomic medicine is defined here as “health applications derived from genomic approaches and research, manifested amongst others, in both boutique personalized medicine and population or sub-population level pharmacogenomics and theragnostics\textsuperscript{17}.”
Incidentally, these investments in genomics and associated technologies echo the 2005 Report by the Task Force on Science, Technology and Innovation, ‘Innovation: applying knowledge in development’, which stated that the investment in- and adoption of- innovative science and technology is crucial to improve the health of populations and stimulate economic development in developing countries. However, in order to capitalize on these large-scale genotyping initiatives, emerging regulatory issues, local barriers to the translation of basic research, as well as commercialization and delivery of the potential products will all need to be addressed. For example, how a developing country chooses to leverage the knowledge output will depend upon the existing research infrastructure; how a developing country chooses to protect the data generated will depend upon the existing legislative, regulatory and governance systems in place and how a developing country chooses to integrate the eventual benefits into its healthcare system will depend on domestic health needs and local regulatory health structure. As a result different strategies may arise from these efforts. Genomic sovereignty for instance, is considered a strategic approach to ownership and access to human genetic materials in South Africa, India and Mexico. However, whether genomic sovereignty is justified over human genetic materials may be considered controversial and lacks comprehensive analysis.

1.2 Statement of the Issue

The purpose of the research described here is to understand the motivations for proposing and undertaking large-scale genotyping projects; understand the mechanisms that developing countries are envisioning or implementing to develop genomic medicine appropriate to their own circumstances; explore the potential for commercialization of the results of such projects; understand the challenges faced and how those challenges are being resolved; and to investigate the emerging potential, ethical, legal, social issues that have arisen or might arise as a result of
these projects. The research described here is part of a larger research project entitled *Human Genomic Variation: Implications for Global Health* that includes several case studies of locally led, large-scale genotyping projects in the developing world. Here, I present a descriptive case study analysis of a large-scale genotyping project documenting human genomic variation in India and a proposed project that did not proceed in South Africa. I also provide an in-depth analysis of genomic sovereignty, a theme that arose in these case studies, as well as in the Mexico, Thailand and HUGO Pan Asian case studies that I collaborated on (for a full description of each of the case studies, please see the Research Design section in Chapter 3; also see Appendix 1 for all of the resulting publications). Lastly, I examine the challenges, opportunities and next steps for genomic medicine in the developing world.

Large-scale genotyping initiatives involve several stages, including the collection of samples (blood, saliva or tissue or combinations thereof), which are subsequently typed (assayed for allelic variation). The samples may or may not be stored along with the electronic data in a genetic database. These databases provide baseline information on human genomic variation, specifically, single nucleotide polymorphisms (SNPs) and in some cases, copy number variation (CNVs) within the local population. Human genomic variation studies are beginning to reveal the correlation between phenotypic and genotypic variation as well as the environment, and will ultimately improve understanding of disease predisposition and drug response within individuals and/or populations. These typically begin with measuring genotypic variation to uncover basic baseline variation, followed by more extensive genome wide disease association studies and

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*As part of a larger Genome Canada Grant ‘Strengthening the Role of Genomics and Global Health, the ‘Human Genomic Variation: Implications for Global Health’ project examined the implications for global health with respect to the emerging trend in applying knowledge of human genomic variation among population groups to understand disease susceptibility and drug response.*
epigenetics, where the more complex relationship between genotype and phenotype are pursued. There are several projects that have been initiated and/or proposed in the developing world; however, there are no comprehensive empirical analyses of these initiatives. The research described here is of significance to those developing countries that are interested in the evolution of genomic studies, particularly in their intersection with public health and as potential sources of economic activity. In this respect, the findings are relevant to: leaders of research institutions; politicians, especially those promoting science and technology, industrial and commercial, and health; legislators considering research funding; individual scientists; investors and small and medium enterprises in the private sector in both industrialized and developing countries; and international organizations interested in how science and technology, and particularly the life sciences can be used to achieve and accelerate health equity and economic development in general.

1.3 Research Questions

The research described here is part of a larger research project entitled Human Genomic Variation: Implications for Global Health. One of the questions that guided this study is “how and why do developing countries engage in locally led, large-scale genotyping initiatives?”

To answer this question, I led the two case studies featured in this dissertation, in India and South Africa. I also collaborated on the data collection, analysis and description of several additional case studies on Mexico, Thailand and the HUGO Pan Asian SNP Consortium, which are incorporated in later chapters of this dissertation (for a full description of each of the case

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vi The ‘Human Genomic Variation: Implications for Global Health’ project was part of the Genome Canada Grant: Strengthening the Role of Genomics and Global Health. To learn more, see: http://www.genomecanada.ca/medias/pdf/en/StrengtheningRole_GenomicsAndGlobalHealth.pdf
research methods section in chapter 3). For each of these case studies, the sub-questions designed to answer the broader question above were as follows:

**Research Questions:**

1. What are the motivations and mechanisms for conducting locally led, large-scale genotyping projects documenting human genomic variation in the developing world?
2. What are the opportunities, next steps and challenges for conducting locally led, large-scale genotyping projects documenting human genomic variation in the developing world?
3. What are the emerging economic, ethical, legal, and social implications of these projects?

As part of the larger project highlighted above, I collaborated on a cross-comparative analysis across all of these case studies that identified several common themes, which are related to the investment in- and development of these large-scale genotyping projects: political will, institutional leadership, knowledge-based economy, local health benefits and genomic sovereignty (see Appendix 1 for the publication). We proposed that together these themes provide a broad roadmap for other developing countries looking to invest in human genomics studies, as per the 2002 recommendation of the World Health Organization. In this dissertation, I provide an in-depth analysis of one of these themes: genomic sovereignty, which also contributes to the broader question outlined above. For the analysis of genomic sovereignty, I designed the following sub-questions:

**Research Questions:**

1. What is the scope and significance of sovereignty as a foundation on which to examine current debates on ownership of- and access to- human genetic material?
2. Is sovereignty over human genetic material justified?

1.4 Significance of the Research

Through the research described here, I aim to build upon the body of knowledge regarding the contribution of genomics to improving health equity and economic wellbeing in the developing world. I achieve this by documenting how infrastructure and capacity are being established around genotyping projects. First by highlighting the driving forces, approaches, opportunities and challenges of conducting locally led large-scale genotyping projects in the developing world. Second by exploring the scope and significance of sovereignty, as a foundation, on which to explore contemporary debates on ownership of- and access to- human genomic material. The long-term goal is to inform the framing of policies, principles and practices for countries in the developing world interested in the intersection of genomics with public health and economic stimulation.

1.5 Dissemination of the Work

Several publications have resulted directly from this research, where I have contributed to the concept and design of the study, data collection and analysis and drafting of the manuscripts.

Publications (peer reviewed)

- **Hardy B** and Séguin B., Singer PA., Daar, AS. (2008) Genomic medicine and developing countries: creating a room of their own. *Nature Reviews Genetics* 9(6):487-93 (Both Hardy and Séguin contributed equally to this publication)


**Conference Papers (Presentations and Posters)**

I have presented the work featured in this dissertation at the following conferences:

• **Hardy B., Séguin B., Singer PA., Daar AS.** Large Scale Genotyping Projects in the Developing World: Genomic Sovereignty. Singapore July 30, 2010. 10th World Congress of Bioethics. *Presentation*

• **Hardy B., Séguin B., Singer PA., Daar AS.** Large Scale Genotyping Projects in the Developing World: Genomic Sovereignty. Amsterdam, Netherlands May 26, 2010. Centre for Society and Genomics. Ten Years After Mapping the Genome Conference. *Presentation*

• **Hardy B., Séguin B., Singer PA., Daar, AS.** Genomic medicine and developing countries: creating a room of their own. Café Scientifique, Montreal, Quebec April 01, 2010. Genome Quebec. *Presentation*

• **Hardy B., Séguin B., Singer PA., Daar AS.** Genomic medicine and developing countries: creating a room of their own. CIHR Canadian Student Health Research Forum (Nominated by IMS Department), June 02-04, 2009, Winnipeg, Manitoba, Canada – *Poster*

• **Hardy B., Séguin B., Singer PA., Daar AS.** Genomic medicine and developing countries: Genomic Sovereignty. Indian Society Human Genetics International Meeting – March 20, 2009, New Delhi, India – Conference *Presentation*

• **Hardy B., Séguin B., Singer PA., Daar AS.** Genomic medicine and developing countries: creating a room of their own. Genome Canada Meeting, Vancouver – Oct. 22-24, 2008, Vancouver, British Columbia, Canada - *Poster*

• **Hardy B., Séguin B., Singer PA., Daar AS.** Genomic medicine and developing countries: creating a room of their own. Human Genome Variation Meeting – Oct. 15-17, 2008, Toronto, Ontario, Canada – Conference *Presentation*
• **Hardy B.,** Séguin B., Singer PA., Daar AS. Genomic medicine and developing countries: creating a room of their own. HUGO Meeting – Sept. 27-28, 2008, Hyderabad, India, *Poster*

• **Hardy B.,** Séguin B., Singer PA., Daar AS. Human genomic variation and South Africa. IMS Scientific Day – May 14, 2008, Toronto, Ontario, Canada – *Poster*

• **Hardy B.,** Séguin B., Singer PA., Daar AS. Human genomic variation and South Africa. GE3LS Genome Canada Symposium – April 28-30, 2008, Calgary, Alberta, Canada – *Poster*

**Symposia and Workshops**

The following symposia and workshops resulted, in part, as a result of the work described in this dissertation and the findings have been incorporated in subsequent draft policies resulting from these symposia.

• Emerging Regulatory Issues in Genomic Medicine, May 21-23, 2008, Mexico City, Mexico
  o Drug Information Association (DIA), INMEGEN, United States Food and Drug Association (FDA), and the McLaughlin-Rotman Centre for Global Health (MRC)
  o Identify synergies and common issues in Genomic Medicine and to develop common approaches to address these issues. The FDA has a major effort in the area of genomics and personalized medicine. It is working with clinicians, the pharmaceutical industry and other regulatory agencies worldwide to integrate genomic medicine into medical practice.

• Symposium on Genomics and the Bioeconomy, May 17, 2010, Montpellier, France
o Human Genome Organization (HUGO), Organization on Economic Cooperation and Development (OECD) and the McLaughlin-Rotman Centre for Global Health (MRC)

o The overall goal of the meeting was to devise the first draft of a policy agenda and recommendations on how genomics can boost the development of the bioeconomy. The symposium examined the advancement of such genomic technologies and related bioinformatics platforms, related economic opportunities in the internet, reconstruction of new organisms and the unlimited opportunities for enterprises to support discovery, production and services in this arena such as biofuels and genetically engineered food products.

1.6 Structure of the Thesis

In chapter 1 of this dissertation, I introduce the debate on whether developing countries should invest in large-scale human genomic sciences and highlight that there have been few empirical analyses describing why and how countries in the developing world are doing so. I also situate the research described here in the dissertation within a larger research project *Human Genomic Variation: Implications for Global Health* and present the overall research question and sub-questions. I also describe the broader significance of the research and its dissemination.

In chapter 2, I provide a comprehensive review of the literature that provides the reader with a brief historical narrative on the field of human genomics and human genomic variation studies globally, focusing on the creation of large scale genetic databases at the local and international level, the potential health benefits and the main ethical, legal and social concerns. Despite the international nature of human genomics, early on there were few locally led initiatives in the developing world, and developing country participation was often limited to the provision of
human genetic material. The World Health Organization’s (WHO) report *Genomics and Global Health* of 2002 and several initial large-scale genotyping projects in the South are highlighted and help develop the line of inquiry for this dissertation. Amidst all of the literature, there is a lack of empirical evidence describing the experiences of locally led human genomic variation studies in the developing world which has led to a critical gap in knowledge. As an illustration, international guidelines and recommendations on human genomics sciences may be limited in their application in the South, specifically regarding economic, ethical, legal and social issues. In chapter 3, I present the series of case studies to address the broad research question of “*how and why do developing countries engage in locally led, large-scale genotyping initiatives?*” I also outline the methodology and methods for data collection and analysis.

In the subsequent chapters, I address the research questions. In chapters 4 and 5 I present case studies previously published as stand-alone journal articles in Nature Reviews Genetics on which I was lead author. Prompted by the gaps in the literature and guided by the overall research question and sub-questions, I analyze the motivations for proposing and undertaking large-scale genotyping projects in India and South Africa; the mechanisms that they are envisioning or implementing to develop genomic medicine appropriate to their own circumstances; and the potential for commercialization of the results of such projects. I also examine the challenges they have faced and how those challenges are being resolved and I investigate the emerging potential, ethical, legal, social issues that have arisen or might arise as a result of these projects.

In chapter 6, I expand upon one of the central ethical, legal and social concerns associated with human genomic variation studies globally: ownership of- and access to human genetic materials. Specifically, I focus on the concept of genomic sovereignty, raised as one of the key themes in the case studies I present in chapters 4 and 5, as well as in several other additional case studies I
collaborated on as part of the larger project: *Human Genomic Variation: Implications for Global Health*. I provide an in-depth analysis of genomic sovereignty and focus on how it may contribute to each country’s aim of achieving health equity through investments in genomic sciences, its relation to heritage and patrimony, and its potential limitations.

In chapter 7, as a wider discussion of all of the case studies I examine the challenges, opportunities and next steps for genomic medicine in the developing world. Finally, in chapter 8, the conclusion, I identify the unique contribution of this dissertation to the literature, outline some of the limitations of the work and make recommendations for areas for future research.
Chapter 2
Literature Review

2

2.1 Introduction

The following section reviews the literature relevant to my thesis topic of large-scale human genotyping projects in the developing world, focusing on emerging trends. The review begins by describing genomics and human genomic variation studies more generally, defining key concepts and terms as the field began to take shape. It then goes on to examine early human genomic variation studies and genetic databases at both the international and national level. The major driving forces behind these projects as well as the economic, ethical, legal and social issues are examined. These projects, mainly in the developed world, have been frequently featured and analyzed in scholarly literature and have influenced a number of policies on human genomic research, including international guidelines and recommendations. Lastly, the literature review looks at the existing literature on large-scale human genomic variation studies in the developing world. While there has been significant debate for why developing countries should invest in genomics, there have been few empirical analyses describing why and how these countries are actually doing so.

Throughout the review, I point to the emerging themes and gaps in the literature that informed the research questions and aims. In an effort to provide the appropriate context for the reader, I will begin with a brief history of genomics and human genomic variation.

2.2 Genomics and Human Genomic Variation

Following the discovery of the structure of deoxyribonucleic acid (DNA) in 1953, developments in the fields of molecular biology and genetics have been exponential. Well-
known drivers of this growth include the development of recombinant DNA techniques in the 1970s and the first complete sequence of the human genome initiated by the Human Genome Project (HGP) in the late 1980s. These developments, along with many others, gave rise to the current field of genomics, defined by the National Human Genome Research Institute (NHGRI) at the National Institute of Health (NIH) in the United States as “the study of the entire genome of an organism, both at the level of the individual and/or a given population. The breadth of the field of genomics is immense, spanning from the complete annotation of the genome to the study of multiple genome-related actions, such as gene regulation. Accordingly, it is also multidisciplinarian in nature, often requiring international collaborative efforts and incorporating many other novel and traditional fields, such as molecular biology, bioinformatics, proteomics, vaccinogenomics, toxicogenomics and transcriptomics.

By 2001, the HGP results, along with a few additional concurrent studies exploring variation across the human genome, confirmed that there are population-specific or frequency differences between human populations. These findings however, were not unexpected, given the long history of studying human diversity (e.g. blood group typing) that began in the early 1900s. The HGP findings also confirmed that genetically, humans are very similar. In fact on average, up to 99.6 percent of my DNA sequence is similar to any other given human sequence. Roughly 85-90 percent of all variation between humans is due to differences between individuals and approximately 10-15 percent is due to differences between populations. Nevertheless, that 10-15 percent has furthered understanding of human evolution and has contributed to bio-medical research. Although postulated earlier studies began to confirm that genetic variation does differ on the basis of geographical ancestry. If you were to compare genes one by one when studying population variation, there does appear to be more diversity within populations than between. However, if alternatively you were to look at several
genes together, correlations emerge that correspond to particular groups that share common geographical ancestry \cite{39,40,43-45}. Daar and Singer (2005) have posited that these advances in geographical ancestry have implications for population-based research, drug development and global health, particularly in the developing world where some might argue it is needed most \cite{11}. For instance, previously shelved therapeutics could be resuscitated and licensed in populations who are not genetically predisposed to the adverse events present in earlier trials. Or who, when stratified, demonstrate efficacy, potentially reducing the cost of treatment in countries which can least afford it \cite{11} (e.g. Bidil \cite{46}, see Appendix 2)\cite{vii}. In addition, pharmaceutical companies in the developing world could capitalize on genotyping technologies and reduce costs, by developing novel therapeutics specifically for sub-populations that are more likely to benefit without adverse events \cite{11}.

To date, there are approximately 16 million known variants with a minor allele frequency of at least one percent, the majority \cite{12} of which are single nucleotide polymorphisms (SNPs) \cite{47}. SNPs are DNA sequence variations that result when a single nucleotide [A (adenine), G (guanine), C (cytosine), T (thymine)] in the genome sequence is altered; estimates suggest that one in every 1200 to 1500 nucleotides may be different in any two humans \cite{48}. Put simply, SNPs are of interest because they can act as markers in the genome, enabling researchers to locate genes along a sequence. As a result, even prior to the completion of the HGP, researchers based in both public institutions and private industry began to amass data for SNPs and by early 2000, in addition to a number of smaller database initiatives, the SNP Consortium, the US National Center for Biotechnology Information (NCBI), and Celera had each already begun to establish

\vii Human diversity is, of course, not limited to genetics and is the reflection of multiple contributing factors, including socio-cultural (e.g. endogamy), environmental and geographic forces, which has raised legitimate concerns regarding the use of geographical ancestry, race and ethnicity to define populations in genomics.
large-scale genetic databases\textsuperscript{32,49-51} with the main difference being whether the databases were public or private.

The SNP Consortium, which was composed of ten pharmaceutical companies and the U.K Wellcome Trust, created a public database of approximately 1.5 million SNPs, which is currently available as data dumps at the dbSNP and the International HapMap Project (HapMap) websites. The Consortium initiated the project based on the belief that such a pre-competitive and publicly accessible tool was vital to innovation in drug development\textsuperscript{52}. NCBI’s dbSNP continues to be managed as a public database of genetic polymorphisms (SNPs and others) that relies upon voluntary submissions (as of build 132, they had amassed over 243 million submissions across 100 species)\textsuperscript{53}. Celera, on the other hand, now a ‘healthcare company’ maintains a private genetic database. It has been strategically designed to maximize internal business opportunities in diagnostics and drug discovery (e.g. they focus on re-sequencing relevant regions of the genome)\textsuperscript{54}. In addition, by 2005, a number of privately held genetic variation databases had also been initiated. ChemGenex, formerly known as Autogen, then AGT Biosciences who merged with ChemGenex in 2004, established a genomic database with approximately 44,000 samples\textsuperscript{55,56}. Another example is the Genomics Collaborative in the U.S., who has created a database with approximately 120,000 samples\textsuperscript{55,56}. Hsieh (2004) and Maschke (2005) pointed out early on that these companies were providing industry, at a cost, with data on genetic variation for drug development research\textsuperscript{55,56}. These rapid advances in the early 2000s provide a snapshot of the rate at which human genetic material was being organized and assembled within both public and private genetic databases.

These initial approaches to sequencing, genotyping and genetic database development are important, because they laid the groundwork for the current debates around informed consent,
privacy and protection of information, property and control and ownership and access of

**genomic information** in human genomic variation studies; debates that continue to this day and that we will review in later sections.

### 2.3 Large-scale Human Genomic Variation Initiatives

**International Projects**

Interest in systematically cataloguing SNP variation, across populations, on a large-scale was initiated in the early 1990s. Cavalli-Sforza and colleagues (1991) proposed that a large-scale catalogue of common genetic variants across the human genome be established to support studies of human evolution and population genetics. Moreover, throughout the HGP, additional requests were made to extend its aim to obtain a catalogue of human genomic variation that was as complete as possible \(^{26,57}\). However, over time, differences in opinion arose amongst the various stakeholders on how this goal could be best achieved.

Among the most well known large-scale genotyping \(^{viii}\) projects proposed were the Human Genome Diversity Project (HGDP) and the HapMap \(^{ix}\). In 1991, the HGDP was proposed to document the global genetic variation of the human species and provide a database for research on human biological migratory history \(^{59}\). It planned to sample up to 500 global populations; acquiring donated samples from each population. These could then be preserved as

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\(^{viii}\) “One's genotype differs subtly from one's genomic sequence. A sequence is an absolute measure of base composition of an individual, or a representative of a species or group; a genotype typically implies a measurement of how an individual differs or is specialized within a group of individuals or a species. So typically, one refers to an individual's genotype with regard to a particular gene of interest and, in polyploid individuals, it refers to what combination of alleles the individual. The genetic constitution of an organism is referred to as its genotype. \(^{56,57}\)"

\(^{ix}\) Another similar anthropological project is the National Genographic Project. Similar to the HGDP in many ways, it has also encountered several challenges and remains controversial amongst various stakeholders. To learn more see: https://genographic.nationalgeographic.com/genographic/index.html.
both cell lines\textsuperscript{x} and stored DNA samples for further analysis \textsuperscript{59}. However, despite an endorsement from the HGP in 1991, the HGDP was severely criticized by various groups, ranging from technical concerns associated with sampling, methods (e.g. creating cell lines) and storage (central versus regional) to socio-cultural and political concerns of bio-piracy, bio-colonialism and scientific racism, which for some time put it at risk of failing \textsuperscript{60-62}. These latter criticisms framed many of the earliest debates on property and control and ownership and access to genetic information. Eventually, the HGDP did proceed and in collaboration with the Centre d’Etude du Polymorphism Humain (CEPH) in France, it now houses a collection of samples obtained from 1050 individuals in 52 global populations (to learn more see, http://www.cephb.fren/hgdp/diversity.php). These are used to understand sequence diversity and the history of human populations. Those researchers who wish to access these samples must be non-profit and are required to provide the results of their studies to the CEPH database in order for the results to be made public to other researchers \textsuperscript{59}. Greely (2001) \textsuperscript{62} and Hsieh (2004) \textsuperscript{55} have both suggested that the HGDP failed to achieve greater status because its focus was anthropological rather than biomedical.

The HapMap, on the other hand, is a multi-country effort between Japan, United Kingdom, Canada, China, Nigeria and the United States that was initiated in 2002. Highly successful, the HapMap aims were primarily biomedical in nature. It sought to guide selection of SNPs to tag common variants towards locating genes that affect health, disease, individual responses to medications and environmental factors \textsuperscript{63,64}. In contrast to the HGDP, the HapMap project took

\textsuperscript{x} The HGDP created lymphoblastoid cell lines which result in indefinite supplies of DNA and are obtained from B lymphocytes, a fraction of white cells from blood that can be grown indefinitely in the laboratory after special treatment of the cells with Epstein-Barr virus \textsuperscript{59} – it is thought that over time, cell lines degrade resulting ultimately in a lower quality resource.
advantage of haplotypes blocks, which are sections of inherited alleles (strongly associated SNPs) found on large chromosomal regions \(^{64,65}\). In 2001, researchers discovered that a limited number of these haplotypes blocks could explain most of the variation across the human genome \(^{66,67}\). These findings reduced the effort and the cost needed to catalogue human genetic variation, as researchers found they could detail sufficient variation by genotyping a few SNPs in each haplotype region of the genome. The consortium chose to focus on three distinct populations which they hypothesized would provide a fair initial description of variation across global populations (Western European, Nigerian and Asian), and within three years the first phase of the project was complete \(^{68}\). The resulting database is a public resource (as per the principles of an international community resource project, which aims to share information rapidly without restrictions upon its use) and lists approximately 10 million DNA variations across the human genome, including both SNPs and CNVs \(^{64,68,69}\).

SNPs, of course, are now only considered to be one piece of the puzzle, other sources of human genomic variation include small insertion-deletion polymorphisms (microsatellites etc.) and structural variants, such as: copy number variants; copy number polymorphisms; segmented duplication or low copy repeats; inversions; translocations; and segmental uni-parental disomy \(^{70-74}\). As such, researchers continue to contribute to the HapMap, in an effort to increase its resolution by accounting for structural variations and extending into additional populations \(^{75,76}\). The HapMap is considered a powerful genomic tool that enables researchers to employ common genomic variants to locate the multiple genes that influence complex common diseases using advanced molecular biology techniques, such as hypothesis driven candidate gene association
studies\textsuperscript{xi} and linkage disequilibrium\textsuperscript{xii} studies, and more recently hypothesis free genome-wide association studies\textsuperscript{xiii} (GWAS)\textsuperscript{65}. Manolio (2008) has pointed out that as of 2008, the HapMap database had enabled the identification of approximately 100 loci for up to 40 complex common diseases and traits\textsuperscript{65}. However, he has also outlined several important limitations in relying on the HapMap: it is not optimal for assessing disease associations with rare variants and structural variants; it requires a large number of samples and the patterns of genomic variation in those populations not included in the HapMap are not optimally described\textsuperscript{65}. This last limitation is a significant one. The estimated size of a haplotype block necessary to capture genetic variation in populations of European or Asian ancestry is \textasciitilde22 kilobases (kb), whereas in populations of recent African ancestry it is \textasciitilde11 kb and within each of the blocks themselves, haplotype diversity varies across populations (e.g. the Yoruba have an average of 5.6 whereas the Han Chinese and Japanese have an average of 4.0)\textsuperscript{65}. As a result, the HapMap’s chosen tag SNPs are limited at capturing genetic variation within populations with recent African ancestry\textsuperscript{79}. Although the HapMap has made efforts to include additional populations samples, most populations remain woefully absent in the HapMap data, as such any research resulting from the resource will reflect this limitation. Notably, Rosenberg and colleagues (2010) demonstrated that approximately 75% of those GWAS studies included in their sample have used populations of European descent\textsuperscript{80}.

\textsuperscript{xi} Association Studies (AS): a method for localizing genes responsible for specific diseases by comparing the DNA of a selected set of patients who are believed to carry the same mutation/s because of their ancestral origin, with that of unrelated health controls from the same population\textsuperscript{59}.

\textsuperscript{xii} Linkage Disequilibrium (LD): a tendency for markers that are physically close to each other on the same chromosome to be transmitted to the progeny together as there is a low probability that they will be split through recombination\textsuperscript{59} – this feature is harnessed in linkage mapping with haplotype blocks, such as the HapMap.

\textsuperscript{xiii} Genome-wide association studies (GWAS): An approach used in genetics research to look for associations between many (typically hundreds of thousands) specific genetic variations (most commonly single-nucleotide polymorphisms) and particular diseases\textsuperscript{77,78}. 
These above-mentioned early large-scale collaborative projects (HGP, HGDP and HapMap) are only part of the effort to generate a complete characterization of human genomic variation. Other more recent studies extend beyond genotyping and include EnCODE, the 1000 Genomes Project and the Perlegen Project.

Together these large-scale projects illustrate two important trends with respect to human genomic variation studies, which have arisen in the post-genomic age. First, these projects prioritized collaboration. Collaborations are becoming increasingly important in human genomic sciences. In part, this is for reasons related to cost and infrastructure, as it is oftentimes not productive for a single laboratory to generate all of the data independently. However, it is also necessary to achieve statistical significance or to gain access to alternative populations. Second, the data generated is, for the most part, considered a pre-competitive public resource, oftentimes being made available as soon as it has been generated. This approach followed on the 1996 Bermuda Principles where the Wellcome Trust, the UK Medical Research Council, the National Institutes of Health National Center for Human Genome Research, the U.S. Department of Energy, the German Human Genome Programme, the European Commission, the Human Genome Organization and the Human Genome Project of Japan endorsed that primary genomic sequences should be rapidly released (i.e. within 24 hours of generation) and remain in the public domain (see: http://www.ornl.gov/sci/techresources/Human_Genome/research/bermuda.shtml). These principles were reaffirmed as the Ft. Lauderdale Principles in January 2003 and extended to all large-scale projects considered as community resource projects (xiv) (see:)

xiv A community resource project is defined by the Ft. Lauderdale Principles as “a research project specifically devised and implemented to create a set of data, reagents or other material whose primary utility will be as a
The principles were further endorsed at other meetings, including, most recently, the Toronto Data Release Workshop in 2009. According to Contreras (2011) who has referred to these principles as the building blocks towards the formation of a “genome commons,” these principles generally incorporated three rationales: facilitating project coordination; achieving scientific advancement; and, minimizing intellectual property encumbrances.

These two trends apply mostly to large-scale international collaborative enterprises such as the HGP and the HapMap, where the data generated was initially defined and released as a public resource for the public good. Moreover, these early data were anonymous. As we shall see though, in similar large-scale population based initiatives established at the national level these principles are more complex. This is in part because many national projects incorporate additional phenotype data, raising additional issues of privacy and protection of information. In addition, despite the collaborative effort and global scale of each of these projects, there is little representation of developing world populations. Although there may have been scientists from the developing world at the First International Strategy Meeting on Human Genome Sequencing in Bermuda in 1996 there are no developing world institutions listed on the endorsement. Moreover, as a result of the lack of scientific capacity and infrastructure, they have frequently participated only as sample donors. Such collaborations can and have been viewed as inequitable. As previously highlighted, the poor representation of developing world populations raises important concerns. For example, it is well known that the richest source of human genomic resource for the broad scientific community” (see: http://www.genome.gov/pages/research/wellcomereport0303.pdf: page 2)
variation is located in sub-Saharan Africa\textsuperscript{90,91} and thus, highly unlikely that a single population (e.g. Yorubans of Nigeria) will capture a representative baseline variation amongst African populations. In addition, both India and Latin and South America were notably absent from the HGP and the HGDP\textsuperscript{xv}. In view of these facts, it is possible, given that human genomic variation aligns with geographic ancestry, that the resulting bio-medical research conducted using these data may not benefit these populations. For instance, genomic diagnostics developed in the United States, Canada or the United Kingdom, using these data, may have limited utility in Tanzania, India or the Philippines. We will return to this limitation later, yet it is important to note that for the most part and despite various recommendations\textsuperscript{3,4,20,22-25,87,92} the genomic revolution had begun to bypass the developing world and generate a genomic divide.

**National Projects**

By 2008, large-scale projects had been initiated at the national level where in addition to DNA samples and/or genomic data, some also included epidemiological and/or genealogical data. These projects have drawn attention to an infrastructure-based trend associated with human genomic variation studies, large-scale genetic databases. As the effort to genotype human genomic variants in large population samples and identify the variants that contribute to complex disease progressed, there were also calls for the additional collection and storage of carefully phenotyped cohorts of patients and healthy individuals\textsuperscript{26,93,94}. In the literature, the term genetic database is often interchangeable with various other terms. For instance, Capron et al (2009) has used the terms ‘biobank’ and ‘genetic databases’ interchangeably to denote “a collection of

\textsuperscript{xv} In discussion with the IGVdb participants, I was told that the HGP had extended an invitation to India to participate in the project, however officials declined due to concerns that the structure of the HGP would not reflect an equitable partnership and instead Indian researchers would provide human genetic materials.
human biological samples that can be used for genetic analysis”⁹⁵. The following is a sample of these two definitions:

- A biobank “is a collection of biological material and the associated data and information stored in an organized system, for a population or a large subset of a population [accessed on January 28, 2010: http://stats.oecd.org/glossary/detail.asp?ID=7220]

- Genetic databases: “tend to be systematically organized collections that typically store human tissue, bodily samples, extracted DNA and/or physical genetic material, together with relevant personal, medical, genealogical, genetic and/or lifestyle data, relating to increasingly large numbers of individual participants.⁹⁶”

As these definitions suggest, genetic databases exist across a spectrum and collections may differ in size, origins, purposes, design features, technical sophistication, content, duration, creation, range of users and ownership. This is best demonstrated by a brief comparison of the UK Biobank and 23andMe, both genetic databases, which differ in each of the above-mentioned features. For instance, 23andMe is a private, direct-to-consumer (DTC) business, which offers consumers a menu of personal genome profiles at varying costs. The individuals are provided with these profiles and offered the chance to participate in an online ancestry community, somewhat akin to Facebook. However, 23andMe also maintains these profiles (along with additional information) in a genomic database accessible to 23andMe as well as third parties at a cost, as a research tool⁹⁷,⁹⁸. On the other hand, the UK Biobank is a not-for-profit genome epidemiology enterprise, which plans to follow up to 500,000 individuals across Britain in an effort to determine the links between genotype, phenotype and environment amongst the British population⁹⁹. These basic differences (e.g. not-for-profit trust versus private-for-profit) reveal that genetic databases have several governance challenges⁹⁶,¹⁰⁰. Of course, tissue and DNA sample storage is nothing new per se¹⁰¹,¹⁰², however what is new is the scale at which these materials are being stored, oftentimes in tandem with additional phenotypic data.
Here, I review the earliest, and most studied genetic database initiatives: deCode’s Iceland database, the Estonian Genome Center, the UK Biobank and the Autogen/Tonga database. Together, these projects were initiated amid a maelstrom of debate and disagreement regarding genetic databases, from which many of the current technical and governance trends have been developed (e.g. the OECD 2006, Creation and Governance of Human Genetic Research Databases Guidelines). A number of the initial projects were framed as gene hunting expeditions in ‘unique’ population groups (e.g. deCODE and the Autogen/Tonga projects), whereas later initiatives were cast as national public health research projects (UK Biobank). These differing approaches are important, because how these projects are framed will, in the long term, influence public opinion and subsequently the level of political will and public funding invested in each initiative.

The Iceland Health Sector Database/deCODE Genetics

In 1998, Iceland’s parliament ratified Act no. 139/1998 on a Health Sector Database that would assemble in digital form, medical records for the entire Icelandic population. That same year, deCODE Genetics, a private biotechnology firm, was granted the license to construct a database incorporating three components (genetic data, genealogical records and health records) ‘the Genealogy, Genotype, Phenotype Resource’ (GGPR) and as sole licensee, was guaranteed privileged rights to commercialize the database for 12 years. In return, it was agreed that deCODE would pay an annual inflation-adjusted payment of $900,000 US plus 6% of its pre-tax profits to the government of Iceland. Estimated in 2002 to have a budget of $212M US, the government of Iceland viewed the project as highly beneficial and suggested that it would lure back research scientists who had left Iceland and that it would benefit Iceland’s economy. Annas (2000) wrote that the government of Iceland should have negotiated a
better deal, as it was unrealistic to expect that scientific benefits would accrue as access to the database was restricted. Shortly thereafter a controversy erupted over consent mechanisms, specifically the employed method of presumed consent that put the onus on Icelandic citizens to ‘opt-out’ should they not wish to have their health records included. Ultimately 20,000 did opt out, however, there is significant evidence that the Icelandic public was generally positive about the project. The project never fully recovered, as fears arose regarding the commodification and commercialization of what some referred to as Iceland’s “genetic heritage.” Subsequently deCODE continued their research without the Iceland Health Sector Database. The Iceland narrative provided many lessons learnt and over the years these have informed international policy on human genomic variation studies (e.g. OECD Guidelines on Biobanks and Genetic Research Databases and various HUGO Statements) as well as stakeholders looking to establish national genetic databases. Indeed, Iceland was one of the first countries to pass a Biobanks Act with specifications on the collection and storage of biological samples. The government defined a biobank as a collection of DNA samples that is permanently preserved and must be licensed through the Minister of Health. The Act states that biological samples cannot be owned by biobank licensees and that “… the utilization of the biological samples serves the purposes of science and medicine, and is conducive to the public good.” Palsson (2007) however, has suggested that there remain significant controversies regarding property, ownership and access as they relate to commodification. He has compared Iceland’s health records and genetic information to Iceland’s fisheries, another ‘common property’ resource that provides an excellent analogy for the debate, as here, the Icelandic

DeCODE established a proprietary genetic, genealogical and phenotypic databases where they obtained the genetic and phenotypic data through traditional informed consent research protocols and genealogical data was obtained through public resources.
government has been criticized for transforming the fisheries into a ‘commoditized resource’\textsuperscript{114,119}. The analysis points to the importance of focusing on the contextual nature of these projects. Currently, deCODE is a private company, headquartered in Iceland which compiles publicly available ancestral data with genomic and epidemiological data donated by consenting adult participants\textsuperscript{109,120}. Likely the most written about private genetic database in existence, with what appears to be lessons to spare, deCODE has recently encountered some fiscal challenges (threat of bankruptcy)\textsuperscript{120}, which is a stark contrast to its estimated market capitalization of $500M US in 1999\textsuperscript{113}. Thus, whether the business model is viable remains to be seen\textsuperscript{120}.

**The Estonian Genome Project**

In 1999, the Republic of Estonia and the Estonian Genome Foundation launched the Estonian Genome Project, a genealogical and genetic database that represents five percent of the Estonian population. The aim is, as with many others, to link genotype, phenotype and environment, eventually towards increasing the efficiency of healthcare in Estonia\textsuperscript{121,122}. As with Iceland, in 2000, the Estonian Parliament enacted accompanying legislation, the *Human Genes Research Act (HGRA)* which dictates the rights of donors, how the data can be processed and stored and prohibits genetic discrimination in employment or insurance\textsuperscript{55,103,123-125}. Unlike the Iceland HSD, the Estonian Genome Project established informed consent and a voluntary participation model and placed the responsibility of collection and processing on the Estonian state (instead of a private company), specifically to avoid similar criticisms and concerns\textsuperscript{123,124,126}. In an effort to engage with- and obtain support of- the public, the Estonian Genome Project will release data to participants who wish to know their genetic risks\textsuperscript{125}. With an initial estimated budget of $150M US\textsuperscript{107}, promoters of the Estonian Genome Project framed it as an important economic investment in the knowledge-based economy, enabling Estonia to emerge as
a progressive democratic nation able to compete in the global economy \(123,127,128\). The project was also initially a public-private partnership with the biotechnology firm EGeen Ltd. Egeen was granted a 25-year, exclusive licensing deal in exchange for an annual payment of $300,000 US, an annual 0.5% profit payment and 3% of turnover for any resulting intellectual property rights \(125\). However, by 2004, the partnership was terminated, largely due to the lack of returns \(122-125\) and the Estonian Genome Project is now a public research venture at the University of Tartu, Estonia with 40,766 participants registered (accessed January 29, 2011 see: [http://www.geenivaramu.ee/index.php?lang=eng](http://www.geenivaramu.ee/index.php?lang=eng)). Since the Estonian Genome Project’s inception, concerns have surfaced regarding the conflicting nature of the database and Estonia’s ability to provide personalized medicine. Early on the Project was criticized as a misallocation of funding, given that Estonia’s health care system is underfunded \(129\). In 2003 an independent poll showed that only 6% of those interviewed were opposed to the project \(124\). However, Sutrop and colleagues (2004) found that 80 percent of participants volunteered in order to obtain a personalized gene card, where one participant was described as saying that despite the diagnosis, they lacked the financial means to obtain necessary treatment \(125\).

**The Autogen/Tonga Database**

In November 2000, Autogen, announced that it had signed an agreement with Tonga’s Ministry of Health to develop a genomic database, which would identify disease-causing genes \(20\). Autogen was a biotechnology company based in Melbourne, Australia, now known as ChemGenex \(55,56\). Under the agreement, Tongans would retain the rights to their genetic samples and Autogen would provide the resource and funding for research in addition to paying out royalties \(20,130-132\). Autogen stated that the main research focus would be diabetes, given that at the time, 14% of the population suffered from diabetes \(20,133\). Autogen also agreed to provide the
therapeutics for free\textsuperscript{20,132}. In 2001, Autogen’s Chairman and Research and Development Directors were quoted as saying that the project would help bolster the country’s medical infrastructure and improve the economy through job creation\textsuperscript{134}. Controversy was immediate, with opposition from the Tonga Human Rights and Democracy Movement because of the lack of public discussion prior to its announcement\textsuperscript{135}, as well as concerns regarding the ethics protocol, commodification of “sanctified blood”\textsuperscript{132}, bio-prospecting and conflicting consent models (e.g. communitarian versus individual)\textsuperscript{20,130,132,135,136}. As a result, by 2002, Tonga’s Ministry of Health denied signing any agreement and Autogen withdrew, effectively terminating the project\textsuperscript{20}. Similar to the HGDP, the proposed Tongan database provides one of the few empirical analyses of human genomic diversity studies in the developing world.

**The UK Biobank**

In 2006, the UK Biobank was launched\textsuperscript{137} as a large-scale nationally-based research initiative with the aim of “improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart disease, diabetes, arthritis and forms of dementia [accessed February 24, 2011 - \url{http://www.ukbiobank.ac.uk/about/what.php}].” It planned to recruit approximately 500,000 individuals, aged 40-69 years and collect and store lifestyle questionnaires, physical measures, and blood and urine samples\textsuperscript{130,137-139}. Informed consent is broad-based and permits for follow-up through linked health-related and medical records\textsuperscript{139}. Modeled after the charitable trust\textsuperscript{140}, it is funded entirely by public monies obtained from the Wellcome Trust, The Medical Research Council, the UK Department of Health, and the Scottish Executive\textsuperscript{99,138}. The UK Biobank had been conceptualized in 1999\textsuperscript{138}, but was delayed because it was difficult to: predict what information would be most useful in the future; to assemble the information system and to recruit the necessary human resources\textsuperscript{141}; there were
also a number of criticisms and concerns regarding consent mechanisms. In addition, GeneWatch UK, a not-for-profit initiative aimed at monitoring developments in genetic technologies, raised concerns early on regarding future use of the information, commercialization and genetic determinism. The UK Biobank attempted to address many of these concerns. In 2000, representatives of the UK Biobank conducted a series of consultative sessions with the general public and specific groups (e.g. disease-based) to help to inform its development. And, in 2003, they provided a draft version of their Ethics and Governance Framework for open comment, from which a final version was adopted in 2006. Currently, the UK Biobank has exceeded expectations and as of November 1, 2010 it had recruited 503,316 individuals [accessed February 24, 2011 - http://www.ukbiobank.ac.uk/about/what.php].

A number of additional projects were initiated other than those four described above: including Biobank Japan launched in 2003, the Latvian Genome Project launched in 2001, Sweden’s UmanGenomics, the Genome Institute of Singapore/Singapore Tissue Network announced in 2002 and Cartagene in Canada. Meanwhile, in the developing world there were a few Northern led, North-South collaborations but more frequently the developing world participated through contributions of human genetic materials to international consortia such as with the HapMap and the HGDP. As of 2003, however, researchers and governments in developing countries, mainly emerging economies, began to propose local and regional large-scale genotyping initiatives. These included Mexico’s National Institute of Genomic Medicine

xvii Examples of early North-South collaborations include, the Jean Dausset Foundation-CEPH that established a national DNA bank in The Gambia, West Africa, focusing on TB, Malaria and HIV; the Kadoorie Study of Chronic Disease (Hong Kong, China and the United Kingdom), and; the Guangzhou Biobank (Hong Kong, China and the United Kingdom). Another example is the impressive Malaria Genomic Epidemiology Network.
Together the international consortia and national projects illustrate two important trends with respect to human genomic variation studies. First, they are confronted with critical challenges. Some of these have been technical in nature, while others are ethical, legal and social (ELS). Often ELS challenges can find analogies in traditional bioethics, however with the focus shifting from the individual to large populations. Knoppers and Chadwick (2005) and others have called for a re-evaluation of the traditional norms in bioethics. Second, these consortia and projects are driven by several factors. Initially, anthropology and historical migration were the aims of these investments whereas now the leading emphasis is on the expected health and economic benefits. The next two sections will focus on these, starting with an overview of the ELS challenges.

2.4 Ethical, Legal, and Social Issues

There are several ELS challenges associated with genetic databases and human genomic variation studies more generally. They can be considered under the following broad trends: privacy and protection of information, informed consent, property and control and ownership and access to information. Although, there is no clear delineation between each heading (privacy and protection of information raises issues of informed consent and vice versa), they highlight the main trends that encompass the ethical, legal and social issues, which have arisen and continue to arise regarding genetic databases and human genomic variation studies generally. Below, I provide a brief summary of each of these trends, highlighting some of the main debates and proposed recommendations.

Privacy and protection of information
Anderlik and Rothstein (2001), in an early paper on privacy and confidentiality of genetic information, state that genetic privacy is both intrinsic and instrumental\textsuperscript{154}. Intrinsic, in that it is derived from the ethical principle of autonomy and instrumental in that it is essential to ensure desired outcomes. For instance, they propose that genetic privacy is instrumental to public health because without it individuals will be hesitant to share their information with health care providers and may forego testing altogether\textsuperscript{154}. However privacy norms may also differ across nations and cultures, making it very difficult to develop a single standard. Regardless, in 2004 researchers demonstrated that with access to only 75 SNPs they were able to identify an individual\textsuperscript{155} and by 2008, it became obvious that available software could isolate individuals’ profiles within genetic information held in genomic databases\textsuperscript{156}. In response, the NIH temporarily removed all genetic data from the web. Still, others managed to demonstrate that specific genetic information would also be difficult to hide by publishing James Watson’s APOE\textsuperscript{xviii} status\textsuperscript{157}. Kosseim and colleagues (2004) have outlined four different normative approaches to genetic information: the personal information approach; the sensitive information approach; health or medical information approach and the genetic information approach. The first three consider genetic information as similar to other forms of data, which, for the most part, already have protocols in place (e.g. banking information or census data). The last option however, accords special status to genetic information and defines what constitutes genetic information, distinguishing it from other types of data. This distinction can give rise to concerns

\textsuperscript{xviii} APOE is short form for apolipoprotein E, a gene for which certain variants may be indicative of various conditions, including: Alzheimers’ and Cardiovascular Disease.
of genetic exceptionalism\textsuperscript{xix} – and raises important concerns as to why one would accord special status to genetic information\textsuperscript{159}. Historically, genealogical information has been publicly available, medical records have been kept in databases and files by the medical community, and statistical databases containing various personal data have been managed by governments. Those who do accord special status to genetic information have raised concerns regarding historical misuse of genetic information (sterilization, eugenics and euthanasia programs) and the unique aspects of genetic information from which potential duties may arise, such as familial obligations as well as the community and population character of the information (e.g. ancestry, migration and disease groups)\textsuperscript{160-163}. Indeed, there is a very real risk of discrimination. For instance in the U.K. under certain circumstances\textsuperscript{164}, insurance underwriters can request genetic test results for Huntington’s disease. Finally, Article 4 in the 2003 UNESCO Declaration on Human Genetic Data states that human genetic information does justify special status as: “they can be predictive of genetic predispositions concerning individuals; they may have a significant impact on the family, including offspring, extending over generations, and in some instances on the whole group to which the person concerned belongs; they may contain information the significance of which is not necessarily known at the time of the collection of the biological samples; and they may have cultural significance for persons or groups”\textsuperscript{165}. Consequently, the Declaration states that, “[d]ue consideration should be given, and where appropriate special protection should be afforded, to human genetic data and to the biological samples”\textsuperscript{165}. Currently, there exist various protective measures and approaches, which have been enacted in an effort to mitigate the concerns associated with the challenge of privacy and protection of personal information. Data can be coded or anonymized in a variety of ways however these are not foolproof\textsuperscript{162,166,167} and a

\textsuperscript{xix} Genetic exceptionalism or determinism is largely the belief that genetic information is unique “because it is predictive, independent of time and shared with ‘blood’ relatives”\textsuperscript{158}. 
gap remains in standardizing the language across genetic databases. National legislation has been enacted at various levels to mitigate the concerns of limited privacy, such as the Genetic Information Non-disclosure Act (GINA) in the United States [accessed on March 19, 2011: http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00493:] and the HGRA in Estonia however their effects are as of yet, unknown. Ultimately, all genetic databases are sensitive to this ELS trend, especially as international collaboration between initiatives is a common feature.

**Informed Consent**

Historically, informed consent has been considered a universal norm (largely based on dignity and autonomy) and entrenched in the Helsinki Declaration. In human subject research, however the very nature of genetic databases introduces a number of new situations; not the least of which are secondary uses of data, a consent requirement that clearly stretches the capacity of informed consent – the question then becomes: does one approach participants each time in order to obtain consent or does one attempt to obtain a more broad consent. There has been significant debate around this subject, both legal and scholarly, as it is difficult to determine how to protect individuals beyond the tenet of informed consent without re-introducing concerns of paternalistic science. Informed consent is complex and varies across jurisdictions because it is influenced by various answers to “fact-specific” questions that will determine the information given, those involved, and the context in which questions are asked. The UK Biobank, deCODE and The Estonia Genome Project have each adopted a broad-based consent model. The HapMap project also employed a broad-based consent model, however the data is de-identified and there is no additional phenotypic data, as the HapMap project is a genotyping initiative to establish baseline variation. Others have proposed that informed consent should be a step-wise process, where “it is seen as an ongoing process between researcher and participant”
given the unpredictable nature of genomic research; a proposal already supported in the Council for International Organizations of Medical Sciences guidelines and UNESCO’s International Declaration on Human Genetic Data. Ultimately however, the debate centers around whether or not, in proceeding with genomic databases, we are lowering the protection for individual interests and putting the emphasis on the public benefit; raising the question of what we consider to be public benefit and the risks we are prepared to engage in to achieve it. In recent years, these arguments have referred to public health frameworks, which prioritize valuable public health research initiatives over individual informed consent.

**Property and Control**

The novel context of a paradigm for doing research on people developed along with the idea that you are doing something which effects them, but when you research on excised tissue or stored data there is a shift. Is the tissue or data a research subject and what is the nature of that ongoing interest? Historically, a property right has been assumed as voluntary, something you assign or transfer. Thus, if you consider human genetic material as property it provides you with a greater ability to control secondary uses of it (e.g. it could be considered a gift, a gift with conditions or even a sale). There is a significant amount of literature around property rights and tissue, both legal and scholarly, and the key concerns seem to centre on commodification (e.g. intellectual property) and commercialization. For example, Ram (2009) has argued that the interests at stake are control, confidentiality, commercialization and access to benefits. Tissue transfer across national borders can be an additional concern at the international level.

For the most part, international and national law do not recognize any property rights when it comes to the human body. Yet, as of the controversial ruling in *Diamond v. Chakrabarty*, it has been possible to obtain patents on isolated DNA sequences in the United States and
elsewhere, as they are considered purified, and thus transformed through the application tools. In the United States, up to 20 percent of human gene sequences are under patent protection. There is a controversial case in the U.S. courts regarding a series of patents on breast cancer genes BRCA1 and 2, filed by Myriad Genetics. If these patents are in fact, overturned, it could establish a precedent that could severely reduce, if not completely eliminate DNA patents. Regardless, as the debates around this issue indicate, we struggle inherently with the claim that donors do, in fact, have control over the types of research and the subsequent commercialization decisions and whether or not donors should receive some type of benefit such as a share of the profits or access to a share of the treatments as indicated by the Courts. Those who have argued against commercialization suggest that it can promote secrecy, data hoarding and manipulation of research outcomes. However, it has also been argued that commercialization of tissue may be necessary. For instance, if we consider other tissue markets (blood and sperm), which are multi-billion dollar markets, then the commodification of tissues is nothing new and in these cases tissue distribution has been made possible by market mechanisms, which facilitate recovery, processing and transportation of tissues. In addition to the concerns of intellectual property and commercialization, Upshur and colleagues (2007) as well as others have argued that globally, existing tissue export regulations are heterogeneous and “ambiguous” at best; and if not addressed, they will create unnecessary restrictions on research.

On the other hand, with respect to the electronic data derived from tissue and stored in databases, the issue is far murkier. In recent years, a number of groups (NIH, Wellcome Trust, Genome Canada, Human Genome Project, and the HapMap, etc.) have generated guidelines regarding data sharing, however, for the most part these are limited to the scientific community and address concerns with respect to publishing and intellectual property rights of the
researchers. When the recommendations do address participants, they tend to be with respect to protecting donor confidentiality, indicating that participants are seen to have a limited on-going interest in the data. There is also little consensus as to what a property claim would be in the case of genetic databases (e.g. a share in the profits or a stake in the commercialization process offer two very different alternatives). Pathmasiri and colleagues (2011) have suggested that intellectual property rights in genetic databases are possible on software, questionnaires and equipment developed for the storage of samples and security; collected data, and subsequent innovative input by those accessing the data and samples\textsuperscript{190}.

**Ownership and access to genetic information**

In 1997, the United Nations Education, Scientific and Cultural Organization (UNESCO), drawing from classic legal theory, declared the human genome ‘the heritage of humanity’ in the Records of the 29\textsuperscript{th} session of the General Conference\textsuperscript{191}. Both the Human Genome Organization (HUGO) and the Council of Europe have since modeled their recommendations and guidelines to incorporate this view\textsuperscript{192}. Knoppers (2001) has written on how the initial proposal was to consider the human genome as the *common heritage of humanity*, under which the “uses must be for purposes consonant with peace; access must be open to those who have a right to it, while the rights of others must be respected, and; sharing must be equal”\textsuperscript{193,194}. Were it to have been considered the *common heritage of mankind*\textsuperscript{xx}, as is the Antarctic seabed and ocean floor and outer space\textsuperscript{195,196}, it would have taken precedence over the role of state sovereignty; of course, for these treaties to be effective, they must be signed by all states, which

\textsuperscript{xx} *Common heritage mankind* is “an international legal concept which conveys equal property interests to all people\textsuperscript{195}; the following principles are most commonly associated with it: no state can appropriate it; all states share in its management; all states share in its benefits; it can only be used for peaceful purposes; and all states must share in its preservation for future generations\textsuperscript{195}. Humanity and Mankind can be considered interchangeable here.
has not been the case for any of the three instances noted above. As it stands, considering the human genome to be the heritage of humanity remains purely symbolic – a concept based upon justice; reflecting the finding that all human genomes are 99.6% similar, thereby belonging to no-one and everyone. As Knoppers and her colleagues (2007) later suggested the human genome is “a global resource, the future of which is of interest to humanity as a whole” 194.

Others drawing from economic theory have stated that genomic knowledge 197-200 and genomic databases 201,202 should be considered a global public good. Busby (2006) however has argued that public good rhetoric is nostalgic and obscures the actual use of genomic databases 203. Miles (2006) has further argued that these approaches could result in ‘bio-colonialism’ or “genetic piracy’ of human genetic materials in developing countries that do not have the resources to carry out the research themselves 8. Indeed, Native American tribes in the United States have specific requirements with respect to ownership and access to genetic information. For instance, they may require control over subsequent uses (and user) of the data and materials, and the return of the data and materials 204. In addition, the position that a genomic database is a global public good, held by the HUGO Ethics Committee 201, denies the possible cultural relation between a population and or an individual with respect to genetic material. Knoppers and colleagues (2006) have disagreed outright with critics, writing that “[a]pocalyptic views on biocolonialism … should not detract from the fact that medical research similar to good health is a public good” 194. Public goods, in economic theory, are those goods, which are both non-rivalrous and non-excludable, and most economists consider public goods as a requirement for efficient economic activity. Generally, one can consider the separation between public and private goods to be somewhat of a spectrum spanning from purely private to purely public. Those goods that are non-rivalrous but excludable are considered club goods, whereas those goods that are non-excludable but rivalrous are considered common pool resources 205. Of
course public goods theory raises several concerns, such as the free rider problem\textsuperscript{xxi} or the prisoner-dilemma\textsuperscript{xxii} indicating the necessary pre-requisites of both ‘shared meaning’ and ‘cooperation’\textsuperscript{205}. The transition from a public good to that of a global public good is largely driven by increasing globalization, increasing international scrutiny, existing inequities between nation-states, increasing economic openness and increasing interdependence. However, global public goods also raise policy concerns of defining prioritization and access\textsuperscript{205}. If genomic knowledge and databases are considered to be global public goods, it is likely that currently, they fall somewhere between a global pure public good (knowledge creation) and a regional club good (information networks). Thorsteinsdottir and colleagues (2003) have pointed out that in order for genomics to be used as a global public good there is a need for access goods, or capacity building, otherwise genomics is at risk of becoming a club good, where only those who can afford access will benefit from the knowledge\textsuperscript{199,200}. They also have acknowledged that there is a distinction to be made between the global production, dissemination and eventual utilization of genomic knowledge\textsuperscript{199,200}, although they do not provide a solution to this dilemma. Stiglitz (1999) accounts for the nature of knowledge as an impure good, suggesting that rents can be justified on the basis of efficiency and equity\textsuperscript{206}.

Smith and colleagues (2004) have written that because developing countries do lack the necessary capacity and infrastructure, they are lagging behind the rest of the world in “harnessing genomics knowledge” which as a result affirms that genomics knowledge is indeed a

\textsuperscript{xxi} The free-rider problem, also known as the tragedy of the commons, arises when a ‘user’ accesses a public good without paying for it – the problem results when there is a subsequent under-production or non-production of the public good, thus the free rider ‘rides’ on the efforts of other users at a cost to all users\textsuperscript{205}.

\textsuperscript{xxii} The prisoner-dilemma arises when ‘users’ do not cooperate, despite it being in their best interests, this can arise due lack of communication or the inability to agree on a common strategy; oftentimes resulting in a sub-optimal strategy\textsuperscript{205}.
club good as opposed to a global public good. What’s more, the fact that developing countries cannot avail themselves of these global public goods, but the very resources within their own populations and environments are being extracted and used by those with club membership gives weight to the earlier criticism of bio-colonialism.

What is not clear in the literature is whether or not genomics knowledge and genetic databases are intermediate or final global public goods; if intermediate, as most seem to implicitly lean, then it is the provision of medical research and public health benefits which are in fact the goods. On the other hand, if it is indeed genomics knowledge/databases, which are the global public good, then they are considered goods in themselves. Each approach would ultimately influence the policy debate on ownership and access to genomic knowledge/databases. Lisa L. Martin (1999) has written that we are entering into a new era of cooperation driven by the economic dilemma of providing global public goods. Here Martin has pointed out the strength of epistemic communities, which can act as advocacy networks driving international cooperation; in the case of genomics however, these communities are frequently made up of ‘disinterested’ scientists. This focus on cooperation is further cemented by Chadwick (2004), who has emphasized that global public goods can be considered a strategic concept, which argues for international collaboration in genomic research; here she has focused on the examples of the HapMap and the SNP Consortium. Langlois (2006) has also stated that global public goods are wholly dependent on international collaboration. However, for the most part, these

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xxiii Haas defines epistemic communities as “...a network of professionals with recognized expertise and competence in a particular domain and an authoritative claim to policy relevant knowledge within that domain or issue-area”

xxiv The Mertonian norms of science argue that scientists act under the auspices of: universalism, disinterestedness, communalism and organized skepticism.
collaborations are promoted and led by epistemic communities of scientists with very little involvement of government at the international and/or state level. This can be considered a failing of the movement to consider genomic knowledge and genomic databases as some consider political processes with national and/or international government backing are the only effective ways to provide public goods\textsuperscript{210}.

Several models for ownership and access to genomic resources that recognize the notion of the human genome as ‘common heritage’ and/or a public good have been recommended, including benefit sharing (as per the Convention on Biological Diversity) and charitable trusts\textsuperscript{140}. The Human Genome Organization has provided guidance on benefit sharing [Accessed on January 20, 2011: see: http://www.hugointernational.org/hugo/benefit.html] and the UK Biobank is modeled somewhat after the charitable trust model [Accessed January 20, 2011 see: http://www.ukbiobank.ac.uk/] initially proposed by Karen Gottlieb (1998)\textsuperscript{211} and further developed by Winickoff (2003)\textsuperscript{140} and Emerson (2011)\textsuperscript{212}. Still there is no universal standard for ownership and access to genomic information and the debate continues on how to best achieve these goals.

In summary, genetic databases that document human genomic variation have been initiated at both the national and international level, and there are subtle differences between the approaches within each level and between levels. For example, as of 2008, some countries have established explicit legislation governing database collections, whereas there is no binding legislation, only recommendations and guidelines at the international level. I have compiled some of the more prevalent of these mentioned in the literature\textsuperscript{56,213 89,214} in Tables 1 and 2 (below).
Table 1. International Guidelines on Genetic Databases

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<tr>
<th>Organization</th>
<th>Guideline</th>
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<tr>
<td>World Medical Association</td>
<td>Declaration of Helsinki (2000)</td>
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<tr>
<td></td>
<td>Declaration of Ethical Considerations regarding Health Databases (2002)</td>
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<tr>
<td>Council of Europe</td>
<td>Recommendation on Human Tissue Banks (1994)</td>
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<td></td>
<td>Convention on Human Rights and Biomedicine (1997)</td>
</tr>
<tr>
<td>UNESCO</td>
<td>International Declaration on Human Genetic Data (2003)</td>
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<td></td>
<td>Universal Declaration on the Human Genome and Human Rights (1997)</td>
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Table 2. National Legislation and Guidelines on Genetic Databases

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<th>National legislation on genomic databases</th>
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<tr>
<td>• United States: Genetic Information Non-disclosure Act (2008)</td>
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<tr>
<td>• Sweden: Act on Biobanks (2002)</td>
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For the most part, these legislation and guidelines have focused on the governance of human genetic materials (sometimes including data) and the associated genetic databases. They generally reflect the challenges associated with the ELS issues discussed earlier. Although these projects also face scientific and technical challenges, in terms of generating consensus, unlike
ELS issues, they have not been as contentious. Further, researchers and institutions have been working towards establishing these standards\textsuperscript{215,216}. For example, in 2004 the Public Population Project in Genomics (P\textsuperscript{3}G) was created as a not-for-profit initiative to establish standards across human genomic databases towards promoting and facilitating international inter-operability and sharing\textsuperscript{216,217} [also see: accessed on March 17, 2011 http://www.p3g.org/secretariat/index.shtml].

Scientific and technological challenges can include: experimental design (assay), data collection and handling (standardization), dealing with data heterogeneity, sample and platform standards, technical standards, data format, managing large data sets, and standards of data sets\textsuperscript{215,217,218}.

As stated earlier, global collaboration is often necessary given the cost and size of the international projects. With national projects, collaborations are often driven by the fact that in order to achieve statistical significance or to gain access to alternative populations, researchers need to combine resources from multiple genomic databases\textsuperscript{83,84,219}. This is increasingly worrisome as human genomic variation research is collaborative in nature – yet there is little legislation in place to protect those individuals who provide these databases with their information beyond their national borders. Accordingly many have called for international consensus and standards in governance for genomic databases based on the belief that the impacts of genomics research are global in nature\textsuperscript{55,89,152,184}, although it has also been recognized that any attempt at consensus will need to be ongoing\textsuperscript{220}. In contrast, Karlsen and colleagues (2009)\textsuperscript{221} as well as others\textsuperscript{101,222} have suggested that consensus is at the very least a difficult attempt, given the differing understandings across nations of these various issues. For instance, Gottweis and Petersen (2008) write: “[w]hat makes biobanks governance a complicated topic is the fact that it is not simply, […] a matter of adopting the right ethical and legal technique and considerations that determine the fate of biobanks in society and the smooth interaction between biobanks and society”\textsuperscript{222}. Along with others\textsuperscript{221,223} they point out that there is a concern of
“technocracy”, a lack of basic political and ethical discourse, in not accounting for the diverse societal and national interests, which inevitably arise in debates around genomic databases \(^{222}\). With these concerns in mind, it is important to also highlight that the above ELS issues have largely evolved through debates and discussion held between stakeholders in the developed world, often incorporating empirical data obtained from studies of initiatives in the developed world (e.g. Iceland and the United Kingdom) with some contributions from developing world voices (e.g. scientific members of existing agencies, such as HUGO). The Malaria Genomic Epidemiology Network (MalariaGEN), a North-South collaboration has made some significant contributions to the literature on obtaining informed consent and property and control \(^{150,224,225}\). Chokshi and colleagues have demonstrated that informed consent in the developing world is “a process rather than a simple one-off matter of signing a form” and that it needs to incorporate community engagement \(^{225}\). They have also argued that North-South consortia “possess complex issues for data sharing and intellectual property” \(^{224}\). Moreover, Andanda (2008) \(^{89}\) has argued that there are several gaps in international and national guidelines on ownership and intellectual property rights that have led to challenges in North-South collaborations. Langat (2005) \(^{185}\) has recommended that there is a need for policy interventions at the national and international level to address the gaps on ownership and access to human genetic materials. It is thus, increasingly important to generate empirical analyses of large scale genotyping initiatives, and human genomic variation studies generally, in the developing world, such as those projects proposed in Mexico, Thailand, India, South Africa and the HUGO Pan Asian consortia, documenting the ELS issues and lessons learnt. Especially given that the features of projects within these countries may require additional considerations on each of these trends beyond those listed above.
2.5 Human Genomic Variation: health benefits and other driving forces

The large-scale human genotyping projects presented in this literature review were initiated for various reasons. Although some researchers hope to use the data to “shed light on where and how natural selection acted during human evolution to shape current human genome diversity” \(^{59}\), by and large these projects are funded because of the belief that they will improve understanding of population variance in disease predisposition, diagnosis and drug response; resulting in significant health benefits, including population screening for disease and disease susceptibility, individual diagnostics, improved understanding of disease mechanisms, personalized therapeutics/healthcare, and drug development thereby opening the door to genomic medicine \(^{xxv}\). Here I focus on two broad areas drawn from the above expected health benefits: public health genomics and pharmacogenomics.

Public health genomics

Public health genomics, a rapidly growing field, is one of the predominant perceived benefits of human genomic variation studies and disease predisposition and diagnosis. In 2006, the Bellagio Group on Public Health Genomics described public health genomics as a “multidisciplinary field concerned with the effective and responsible translation of genome-based knowledge and technologies to improve population health” \(^{227}\). Public health genomics involves amassing genetic variation data and its relationship to diseases across populations;

\(^{xxv}\) Genomic medicine is defined as health applications derived from genomic approaches and research, manifested, amongst others, in both boutique personalized medicine and population or sub-population level pharmacogenetics/pharmacogenomics and theragnostics \(^{17}\); where theragnostics is a union of therapy with a diagnostic that can determine the presence of a series of predictive biomarkers, including genomic, metabolomic and proteomic markers; enabling clinicians and physicians to limit the number of adverse drug reactions and refine treatments for patients \(^{226}\).
employing this data towards strategies that both promote health and prevent disease in various populations and targeting and evaluating population-based interventions. The vast majority of current healthcare dollars in the developed world (e.g. United Kingdom, United States, Japan and Canada) go towards treating late-stage illness and disease; some health care experts argue that these dollars would be better invested at the preventative stage [see also: accessed on March 17, 2011: http://www.who.int/mediacentre/factsheets/fs172/en/index.html]. Improving our understanding of disease predisposition and its risk factors through human genomic variation studies will contribute to the development of diagnostics, which will predict disease, at best before the disease manifests, at the very least during the earliest stages of the disease. For example, predictive diagnostics would allow individuals to modify their environment and enable clinicians to begin early therapy or targeted screenings. Indeed, until very recently, most knowledge about the genetic underpinnings of disease was with respect to highly penetrant, high-risk alleles and monogenic diseases, such as Huntington’s, familial Hypercholesterolemia and Cystic Fibrosis. Research into monogenic disorders has led to greater understanding of these diseases, and in some cases has led to the development of novel therapeutics, such as familial hypercholesterolemia and statins. However, complex chronic diseases, such as cancer, asthma, schizophrenia and cardiovascular disease are the leading causes of death and illness and as such the biggest drain on health care resources in the developed world; and they are the result of multiple genetic interactions. Thus, human genomic variation studies could assist in developing the tools necessary to predict disease predisposition. Recent studies have linked numerous genomic variants related to these diseases and since the completion of the HGP and the HapMap, there are more being discovered every week [see: http://www.genome.gov/ResearchAtNHGRI/]. For instance, genetic databases have contributed to the identification of breast cancer genes, the association between infection with H. pylori and
gastric carcinoma and the causal relationship between human papilloma virus and cervical cancer and the link between Epstein Barr and multiple sclerosis. As research progresses, it will be possible to stratify risk to guide public health interventions, expand current understandings of the environmental causes of diseases and develop highly effective prevention guidelines.

However, early on, Burke and colleagues (2006) pointed out that given the high incidence of false-positives among associations of genetic variants and disease, before any clinical applications are considered, all the knowledge about a given set of gene variants will need to be assessed, including prevalence in various populations, strength of the association, and the social and environmental data. Despite these perceived benefits, Holtzman (2006) and Rogowski and colleagues (2009) recommend caution, as for many, the adoption of public health genomics may necessitate an effective national public health care system and there will inevitably be tensions between the high costs of genetic tests and screening, for instance, and scarce resources. So far, in the United States and Europe, there have been significant efforts to adapt genetic information to public health. Indeed, Khoury and colleagues (2007) developed a framework with four phases for the translation of genomics into public health: (phase 1) discovery to candidate health application; (phase 2) health application to evidence-based practice guidelines; (phase 3) practice guidelines to health practice, and; (phase 4) practice to population health impact. And at the national level, the Center for Disease Control has established the Human Genome Epidemiology Network (HuGENet) to translate genomic research into genomic medicine and public health benefits, and the Evaluation of Genomic Applications in Practice and Prevention [EGAPP] Initiative to facilitate translation of genomic-based technologies from research to clinic, using evidence-based assessments. Whereas, at the international level, the European Commission has established the Public health Genomics European Network (PHGEN II) to advise on health
policies and the integration of genomic research into the clinic and GRAPH Int (http://www.graphint.org/ver2/) was formed with the objective of acting as an “international forum for dialogue and collaboration (…) [for the] effective translation of genome-based knowledge for the benefit of population health”.

**Pharmacogenomics**

Adverse drug reactions can be a major cost to the healthcare system and are in part due to inherited variation in individual drug response. Pharmacogenetics is the study of DNA sequence variation as it relates to differential drug response in individuals or populations (includes disposition, safety, efficacy). It emerged as a field in the 1950s following the observation of inherited variation in response to treatment with the muscle relaxant, succinylcholine as well as the anti-tuberculosis drug, isoniazid. There are two main sources of inherited variation that can impact the efficacy and toxicity of therapeutics: *pharmacokinetic* variants, which affect the absorption, distribution, metabolism and excretion (ADME) of a drug and *pharmacodynamic* variants, which affect the biological function of the drug at the site of action. There are a number of monogenic, highly penetrant inherited variations which impact drug metabolism. Two well known are the cytochrome P450 2D6 (CYP2D6) and thiopurine S-methyltransferase (TPMT) genetic polymorphisms, which are both considered pharmacokinetic variants. CYP2D6, is well studied and catalyzes numerous therapeutics, including: tricyclic antidepressants, antihypertensives and antiarrhythmic beta-blockers and the analgesic codeine. TPMT, on the other hand, catalyzes the S-methylation of thiopurine drugs, which are used to treat childhood leukemia, inflammatory bowel disease, and organ transplant recipients. More recently however, the focus has been on pharmacogenomics, which refers to the application of genomics to the study of human variability.
in drug response and/or drug susceptibility (at either the individual or population level); given that pharmacological effects of drugs are often the result of multiple genes [248-250,253] [See also: http://www.who.int/medicines/publications/druginformation/issues/22_1_2008.pdf; accessed January 23, 2011].

It is expected that, in the short term, pharmacogenomics can tailor the administration of drugs to improve safety and efficacy through the identification of responders and non-responders to medication; avoiding adverse events and optimizing dosage; oftentimes referred to as individualized or personalized medicine. Indeed, in 2001, Phillips and colleagues demonstrated that of 27 drugs frequently cited in adverse drug reactions in the U.S., 59 percent were metabolized by a minimum of one enzyme with a variant allele known to cause poor metabolism [254]. Currently, one of the more compelling examples of this argument is with respect to the anticoagulant therapeutic Warfarin, which can have serious adverse reactions, including hemorrhage and excessive coagulation [250,255]. The CYP2C9 and VKORC1 genotypes explain approximately 30 to 40 percent of the pharmacokinetic and pharmacodynamic variation in response to Warfarin, with CYP4F2 also implicated [255,256]. And in a landmark study, where genetic information on CYP2C9 and VKORC1 were made available to prescribing physicians versus a standard control group, hospitalizations for hemorrhage were 28 percent less common for the group in which the genetic data were made available [255,257]. Although Eckman and colleagues (2009) [258] have argued that genotyping patients prior to warfarin therapy may not be cost-effective, the FDA has revised the warfarin label to include genotype-specific dosage information and recommendations that they be considered when prescribing [255]. Indeed, in recent years, the Food and Drug Administration (FDA) has become a major driver of pharmacogenomics in the United States as it has begun to include clinically relevant pharmacogenomic variants on the labels of FDA-approved drugs, such as Warfarin (CYP2C9 and VKORC1), Mercaptopurine (TPMT), and

It is also expected that pharmacogenomics will boost drug discovery and development through the identification of novel drug targets and the development of sub-population specific therapeutics; resulting in potential economic benefits as well as health.\(^{226,252,259-261}\). Although these statements have been tempered in recent years\(^ {262}\).

**Additional driving forces**

There are other significant driving forces behind increasing investments in human genomic variation and genomic medicine other than potential health benefits. A few of these have been described by Daar and Singer (2005) and they include: regulatory incentives\(^ {263-272}\).[See also: Accessed February 21, 2011 - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079851.pdf], recent legislation (e.g. Genetic Information Non-Discrimination Act (GINA)\(^ {xxvi}\) and the Genomics and Personalized Medicine Act (GPMA)\(^ {xxvii}\)), increasing biomarker validation

\(^{xxvi}\) The Genetic Information Non-discrimination Act of 2008 is a Federal law that prohibits discrimination in health coverage and employment based on genetic information. The statute itself defines ‘genetic information’ as information about: an individual’s genetic tests (including genetic tests done as part of a research study); genetic tests of the individual’s family members (defined as dependents and up to and including 4th degree relatives); genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology; the manifestation of a disease or disorder in family members (family history); any request, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or family member. Genetic information does not include information about the sex or age of any individual [See: accessed on March 19, 2011: http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00493:].

\(^{xxvii}\) In 2006, then-U.S. Senator Barack Obama introduced the Genomics and Personalized Medicine Act (GPMA) as s.3822 (1) and again, with the co-sponsorship of U.S. Senator Richard Burr (R-North Carolina), in 2007 as s.976 (2). Recently re-introduced in 2010, the bill outlines measures that bolster governmental oversight and create
These driving forces mainly represent human genomic variation studies in the developed world for the developed world, and as already stated, empirical data from these projects has informed policy at both the national as well as at the international level. As of 2002, there have been increased recommendations that the countries in the developing world invest in genomics. In particular human genomic variation studies have been posited by Séguin and colleagues (2007) as “critical for global health”. Yet, there is little empirical analyses of these activities in the developing world. Empirical analysis of large-scale human genomic variation studies in the developing world is necessary as it can provide a source of ‘real world’ description and analysis, and can inform the framing of policies, principles and practices in human genomic research. The projects that are currently underway in Mexico, India, Thailand and Pan-Asia are admittedly located in the emerging economies of the developing world; however the lessons learnt by these initiatives are more likely to apply to other less developed countries given their shared demographics.
2.6 Human Genomic Variation: the developing world

In 1996, Sergio Pena of Brazil provided three compelling reasons as to how those in the developing world could benefit from genomics. First, greater than 70 percent of the global population is in the developing world. Second, there is an ever-present burden of infectious and parasitic diseases in developing countries that could benefit from genomic medicine. Third, economic and social development through the judicious adoption of science and technology could take place. Brazil, which has long been considered a leader in genomic sciences in the developing world, has invested in cancer genomics (see: http://www.who.int/genomics/professionals/applications/brazil/en/index.html) and the sequencing of parasite and plant genomes. Specifically, in 2001 the Organization of Nucleotide Sequencing and Analysis (ONSA), in Sao Paulo, Brazil, completed the first published sequence of the *Xylella fastidiosa* bacterium, a plant pathogen responsible for disease in economically important crops, such as citrus. Estimates suggest that the *Xylella* bacteria cost the Brazilian economy more than $100 million/year at the time. This effort was accomplished through a network of 200 researchers based at 30 separate laboratories across the country and is responsible in large part for establishing the subsequent capacity in genomic sciences in Brazil that has brought moderate economic benefits. Alellyx, for instance, is a biotechnology company, which spun out of the ONSA network in 2002 and focuses on crops, which are of economic importance to Brazil. Alellyx also holds, amongst others, the US patent on the whole genome and gene sequences for disease diagnostics of *X. fastidiosa*, which they are currently using to develop disease resistance and pesticide research. The company is private, and as such, its revenues are not publicly available but as of 2011 the company employed up to 140 employees, “most of whom are scientists and technicians”.
demonstrating a direct correlation between investment in genomics and economic benefit in an emerging economy. Of course, Brazil is not alone in aggressively pursuing genomic sciences to gain entrance into the global economy. China and Nigeria were both participants in the HapMap\textsuperscript{64,68}. China was also a participant in the HGP, largely invited as the Chinese Ministry of Science and Technology had already created the Chinese National Human Genome Centre (CHGC) and the Beijing Institute of Genomics (BGI) in 1998\textsuperscript{20}. Likely, as a result of these investments, China found itself responsible for characterizing one percent of the human genome sequence towards the HGP\textsuperscript{20}. Since that time, BGI has become one of the leading sequencing centres in the world, and its accomplishments are featured on a number of Nature covers. Today, China is considered a leader in sequencing and bioinformatics\textsuperscript{288}.

Pena’s early thoughts were also given further credence in 2002 in a report released by the World Health Organization (WHO) entitled: \textit{Genomics and World Health}\textsuperscript{20}, where the authors outlined many of the issues which need to be addressed to ensure that all nations (both developed and developing) will benefit from genomics and associated genome-based technologies. In the report, the authors urged developing countries “to strengthen existing, or establish new centres and institutions engaged in genomics research with a view to strengthening national capacity and accelerating application of the advances in genomics relevant to countries’ health problems”\textsuperscript{20}. The report further suggested that, despite the high costs associated with the initial development and implementation of genomics and genome-based technologies, the resulting cost efficiencies to a country’s health care system would be considerable. As a result, they suggested that, developing countries should leverage both north-south and south-south collaborations as well as regional networking opportunities in an effort to access these benefits\textsuperscript{20}. This statement was later echoed by Davila and colleagues (2004), who pointed out that without such collaborative efforts, vital capacity developments, such as that which occurred so successfully in Brazil would not be
replicated in other developing countries\textsuperscript{289}. Yet, Davila and colleagues (2004) also have acknowledged that developing countries continue to be underrepresented in international efforts to sequence tropical disease pathogen and vector diversity. They suggested this is a concern that deserves attention as many relevant neglected infectious disease agents will not be addressed at all by developed world researchers and will rely entirely on the initiative of researchers in the developing world who lack the necessary capacity\textsuperscript{289}. The WHO Report also wrote that these efforts will require particular attention to ensuring that developing countries are able to “evolve the structure” (e.g. pharmaceutical and related industries) to effectively benefit. Otherwise, argued the authors, the gap in the quality of health care between developing and developed nations will continue to widen\textsuperscript{20}. This was demonstrated by the fact that in 2000, 80 percent of all investment in genomics was in the United states where 80 percent of all patents in genomics were filed between 1980 and 1993\textsuperscript{23,24}. Moreover, the developing world has continued to act primarily as a rich resource of biological materials and genetics research, with most of the research being sponsored by governments and institutions located in the developed world\textsuperscript{88,87,290}; oftentimes referred to as “postal research” or “parachute research”\textsuperscript{88}.

It has also been implied by some that developing countries do not stand to benefit from genomics and genomic-based technologies because of the challenges associated with their cost, as well as the lack of capacity and infrastructure\textsuperscript{7,8}. Market segmentation trends for example, may result in unaffordable diagnostics and therapeutics and pharmacogenomics-based products with limited accessibility thereby increasing global health disparities. These critics have suggested that developing countries would be better served by focusing their limited resources on more immediate concerns, such as poverty, access to medicines, and clean water\textsuperscript{7,8}. Drug development however, has traditionally occurred in Western populations with little concern on how drugs can be used or accessed globally\textsuperscript{9,10}. As such, it is imperative that developing countries understand
how their populations respond to disease and therapeutics if they are to avoid further increases in health disparities. Moreover, Daar and Singer (2005) and Séquin and colleagues (2007) have argued that developing countries can least afford to waste precious resources on ineffective diagnostics and therapies\textsuperscript{11,12}. Thus, it is more than likely that genomic and genomic-based technologies will have significant relevance to the health of people in developing countries.

These criticisms also go against the aforementioned WHO Report (2002) that has cited clear examples of how genomics can improve the health of those in the developing world. For instance, the authors pointed out that DNA-based diagnostics for the hemoglobin disorders, thalassaemia and sickle cell disease have provided an excellent example of how the developing world was already benefitting from clinical genetics (e.g. genetic screening and testing programs)\textsuperscript{20}. Indeed, Weatherall (2003) wrote that as of 2003 in Thailand, there were an estimated 10,000 children born each year with Thalassemia and that at the time, the total number of cases was estimated to be between 50 to 75 million, and growing; reflecting an inevitable increase in costs to healthcare in the country\textsuperscript{25}. He argued that the successful development of DNA diagnostics that recognized the variation across populations, and pre-natal diagnosis of hemoglobin disorders had led to a decrease in their incidence in India and southeast-Asia\textsuperscript{25}.

Moreover, the WHO Report (2002) stated that genomics will further benefit the developing world initially through improving understanding infectious disease, such as inherited protective immunity from malaria, tuberculosis and HIV/AIDS, as well as pharmacogenomics. Table 3 is a table reproduced from the WHO Report (2002) that represents the data on human genes involved in varying susceptibility to infectious disease (see below)\textsuperscript{20}. Since then, a number of other candidates have been identified for malaria\textsuperscript{91,291,292}, tuberculosis\textsuperscript{91,293-307} and HIV/AIDS\textsuperscript{91,308-314}. Initially through linkage mapping and association studies and more recently, using GWAS.
Table 3. Examples of Human Genes Involved in Varying Susceptibility to Communicable Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genes Influencing Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>α-globin; β-globin; Duffy chemokine receptor; G6PD; Blood group 0; Erythrocyte band 3; HLA-B; HLA-DR; TNF; ICAM-1; Spectrin; Glycophorin A; Glycophorin B; CD36</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>HLA-A; HLA-DR; SLC11A1; VDR; IFNyR1</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>CCR5; CCR2; IL-10</td>
</tr>
<tr>
<td>Leprosy</td>
<td>HLA-DR</td>
</tr>
<tr>
<td>Hepatitis-B</td>
<td>HLA-DR; IL-10</td>
</tr>
<tr>
<td>Acute bacterial infection</td>
<td>MBL-2; FCγRII-R; Sec 2</td>
</tr>
</tbody>
</table>

G6PD: glucose 6 phosphate deficiency  
TNF: tumour necrosis factor  
ICAM: intercellular adhesion network  
SLC11A1: solute carrier family 11, member 1  
VRD: vitamin D receptor  
CCR-5: chemokine receptor 5  
IL-10: interleukin 10  
IFNyR1: interferon γ receptor 1  
MBL: mannose binding lectin  
FCγRII-R: receptor for constant region of immunoglobulin  
Sec: secretor of blood group substance


The WHO Report (2002) argued that understanding the role of the following genes in susceptibility will ultimately contribute to the development of novel diagnostics, vaccines and therapeutics and knowledge of how they vary across populations will also prove invaluable when conducting clinical trials in these regions. Indeed, given that as of 2004, only 21 new drugs from the 1556 new chemical entities marketed have been indicated for neglected diseases, which include almost all infectious disease in the developing world, investments in genomics will be critical towards addressing this gap.
Early on, pharmacogenomics demonstrated that the multi-drug resistance gene \((MDR1)\) polymorphism involved in the expression of P-glycoprotein could reduce the efficacy of protease inhibitors and other HIV/AIDS treatments \(^{316}\). Importantly Schaeffeler and colleagues (2001) have shown that the frequency of the polymorphism is far greater in West Africans and African Americans, than in European or Japanese populations \(^{316}\). This has obvious implications, given the high rates of HIV/AIDs in African countries and the desperate need for affordable and effective treatments. In addition, in most developing countries, HIV/AIDS standard treatment, if accessible is highly active antiretroviral treatments (HAART). However, the cocktail is associated with several severe adverse reactions. Vidal and colleagues (2010) \(^{317}\) have summarized these adverse reactions along with the relevant pharmacogenomic variants. Table 4 (below) is reproduced from their paper available at [http://aidsreviews.com/files/2010_12_1_015-030.pdf](http://aidsreviews.com/files/2010_12_1_015-030.pdf).

**Table 4. Some Adverse Effects of HAART, the drugs presumably involved and the main genetic variants that have been studied \(^{317}\).**
There are also concerns surfacing regarding increasing resistance to HAART, and Wayengera and colleagues (2008) have identified pharmacogenomics as a key tool to ensure that individuals are receiving accurate dosing. The argument is clear: reducing resistance will provide significant cost-savings to already resource-limited settings. Another significant example of the value of pharmacogenomics in the developing world is Pharmacogenomics for Every Nation (PGENI), a program initiated by Dr. Howard McLeod in the United States, but largely managed through nine regional centres across the developed and developing world (see: http://pgeni.unc.edu/). The main argument for PGENI lies in the fact that most testing is conducted in populations of European ancestry. Thus the majority of safety and prescribing data for most available therapeutics has been approved by the FDA and the European Medicines Agency (EMEA) and is not necessarily relevant for the majority of other global populations.
Although the creators of PGENI admit that population-based pharmacogenomics is not the ideal solution, they suggest that it is the best possible solution, given the available resources. PGENI aims to: “promote the integration of genetic information into public health decision making process; enhance the understanding of pharmacogenetics in the developing world; provide guidelines for medication prioritization for individual countries using pharmacogenetic information collected into public health decision making\textsuperscript{10}. For instance, the polymorphisms of \textit{CYP2C8} are associated with anti-malarial drug amodiaquine hepatotoxicity\textsuperscript{319-321}. In 2005, Cavaco and colleagues demonstrated that approximately 3.6\% of those tested in Zanzibar were homozygous for slow metabolizer alleles\textsuperscript{320}. To date, PGENI has generated significant data on pharmacogenomic variation across populations across the developing world towards more effectively prioritizing therapeutics on the WHO essential medicines list and national drug formulary policies in the developing world\textsuperscript{10,322}.

Daar and Singer (2005) have also provided suggestions as to how pharmacogenomics may prove to be a boon to local private sector stakeholders, small to medium enterprises (SMEs) based in biotechnology, in developing nations. They have intimated that pharmaceutical companies in the developing world could license previously shelved drugs and develop them both for local populations and for others in the developing world who are either not genetically predisposed to the adverse effects or for whom efficacy can be demonstrated to a greater extent. They have also posited that pharmaceutical companies in the developing world could capitalize on emerging trends in genotyping by developing drugs for specific sub-populations that are more likely to benefit without adverse effects. Finally, they have suggested that compounds discovered in the laboratories of developing countries could be of interest to pharmaceutical companies in the developed world if they are relevant to selected minority sub-populations living in developed nations, leading to potentially beneficial partnerships between firms\textsuperscript{11}.
In addition, in the longer term, it is expected that human genomics sciences will also further knowledge of chronic disease

Although infectious disease continues to be the leading health burden in least developing countries, increasingly non-communicable diseases are also becoming a factor; and amongst the populous, emerging economies of India, Mexico and China, they (e.g. heart disease and cancers) are oftentimes the leading cause of death and are expected to increasingly become so in Africa. To date, there are a handful of successful North-South collaborations investigating human genomic variation and chronic disease. For instance, the Africa America Diabetes Mellitus (AADM) study has revealed several new variants related to diabetes as documented by Rotimi and colleagues (2001) and others. Despite the early stages of genomic research on chronic non-communicable diseases, it will be vital that developing nations can affordably access the benefits of research in this growing sector; and even more importantly, that the resulting diagnostics and therapies are effective in their populations.

Minakshi Bhardwaj (2004) has written that given the numerous implications of genetic databases, especially in developing countries where the basic challenges of illiteracy and poverty are still daily challenges, researchers will need to be sensitive to context. She has listed concerns with accessibility and the digital divide; public awareness and understanding; research funding; health care delivery; regulatory procedures and ethical guidelines. Finally, she proposed that these investments categorize research priorities “so that minimum resources can be allocated for better outcomes”. Although she agreed that international harmonization and standardization are important, she has also advised that each developing country will need to weigh the global implications carefully, given the long history of discrimination and exploitation of biodiversity in their countries.
Indeed, emerging economy countries such as India, Mexico and Thailand have each chosen to publicly fund large-scale national human genotyping initiatives exploring human genomic diversity in their respective populations. They have proposed compelling reasons to pursue these initiatives. They have suggested, as in developed countries, that establishing these databases will enable them to access the benefits associated with genomic medicine and pharmacogenomics, which they may otherwise not benefit from because of the personalized nature of the resulting technologies. They went on to suggest that these technologies have the potential to provide cost-savings in drug development; reduce healthcare costs; stimulate growth and investment within the local private sector; and uncover genetic diversity relevant to drug response or disease predisposition. Incidentally, these recommendations to invest in genomics and associated technologies echo the 2005 Report by the Task Force on Science, Technology and Innovation, ‘Innovation: applying knowledge in development’, which, has stated that the investment in- and adoption of innovative science and technology is crucial to improve the health of populations and stimulate economic development in developing countries.

2.7 Summary

This literature review has explored the evolving trends in human genomic variation studies. It has illustrated the evolution from basic human diversity studies, the sequencing of the human genome, large-scale human genotyping studies and associated genetic databases, as well as the associated economic, ethical, legal and social concerns. It has also defined key concepts in the fields of human genomic variation and genomic medicine. Several trends have been highlighted throughout. First, there are large-scale human genotyping initiatives, at both the national and international scale, and those that have been empirically studied have largely come about as a result of expected health and economic benefits. They have also been driven by
additional factors, such as FDA regulation and patient litigation. In addition, these initiatives have encountered significant ELS issues. Some that reflect the traditional bioethical concerns of informed consent and privacy and others that are further amplified by the unique collaborative nature of these types of ‘big science’ research initiatives. Subsequently, over the last decade or so, some countries have enacted explicit legislation at the national level and several international agencies have generated recommendations and guidelines with respect to governance of human genomic variation studies and genetic databases. These motivations and challenges largely reflect initiatives in the developed world, and up until 2008, there had been little empirical analyses of initiatives in the developing world. This is despite the fact that the WHO and others had, very early on, recommended that developing nations invest in genomics, including human genomic variation studies, lest the gap in the quality of health care between developing and developed nations continues to widen. Indeed, as of 2006, despite ongoing international initiatives, developing nation populations in Africa, Latin and South America and Asia were still underrepresented and as such, they were likely not going to be able to avail themselves of all of the expected health benefits generated from the research conducted using the existing genetic databases. At the same time, some even chose to criticize the WHO recommendations, maintaining that human genomic variation initiatives and large-scale genomics should not be prioritized by developing world governments, given what they considered to be the more immediate concerns of poverty, access to medicines and clean water.

Regardless, beginning in 2003, several locally driven large scale genotyping initiatives had been proposed and/or initiated in the developing world, the Indian Genome Variation database, The African Genome Education Initiative and the Division of Human Genetics at Cape Town University, Mexico’s National Institute of Genomic Medicine, The Thai SNP Discovery Project and the Thailand Pharmacogenomic Project and the HUGO Pan Asian SNP Consortium. Each of
these initiatives provides a unique opportunity to incorporate lessons learnt about the motivations and challenges associated with each initiative, towards generating a framework for human genomic variation studies in the developing world. And also, contributing to achieving harmonization in international collaboration in human genomic variation research. Moreover in order for developing countries to capitalize on these large-scale genotyping initiatives and their expected benefits, emerging regulatory issues, local barriers to the translation of basic research, as well as commercialization and delivery of the potential products will need to be addressed. For example, how a developing country chooses to leverage the knowledge output will depend upon the existing research infrastructure; how a developing country chooses to protect the data generated will depend upon the existing legislative, regulatory and governance systems in place and how a developing country chooses to integrate the eventual benefits into its healthcare system will depend on domestic health needs and local regulatory health structure. As a result different strategies may arise from these efforts, providing unique models for other developing countries, with limited resources to emulate. Of particular interest, is how each of these countries, and developing countries generally, considers the protection of human genomic material and the knowledge generated from it; many of these countries are in fact home to unique population resources. The research proposed here aims to contribute to these gaps. First, through exploratory case study analyses of two proposed large-scale genotyping projects: one in India and the other in South Africa. Second, through an analysis of genomic sovereignty, a theme that arose in a cross comparative analysis of the case studies in Mexico, India, Thailand, South Africa and Pan-Asia.
Chapter 3
Methodology

3

3.1 Introduction

In this chapter, I present the research methodology. The chapter starts with a detailed discussion of the theoretical framework for this research, followed by a review over the rationale for case study research. It then outlines the methods for data collection and analysis, including an examination of the validity and limitations of the chosen methods. The chapter concludes with a brief discussion of the ethical considerations for this research. The research described here is part of a larger research project entitled *Human Genomic Variation: Implications for Global Health* that includes several case studies of locally led, large-scale genotyping projects in the developing world. In this dissertation, I present two of the descriptive case study analyses, which I led and that have already been peer-reviewed and published by Nature Reviews Genetics. The first case study is a large-scale genotyping project documenting human genomic variation in India and the second case study is a proposed project in South Africa. In the face of several challenges the South Africa project did not proceed, however I took to the opportunity to speak to those involved and scope out existing activity. I also provide an in-depth analysis of genomic sovereignty, a theme that arose in these case studies, as well as in additional case studies I have collaborated on of Mexico, Thailand and HUGO Pan Asian Consortium (see Appendix 1 for the resulting publications). Lastly, I present an examination of the challenges, opportunities and next steps for genomic medicine in the developing world based upon a cross-comparative analysis I conducted across all of these case studies that has also been peer-reviewed and published in Nature Reviews Genetics (see Appendix 1 for the resulting publications).
3.2 Theoretical Framework

The research described here takes a predominantly naturalistic worldview grounded in empirical observation (qualitative case study research). It also incorporates a social-constructivist worldview (conceptual; qualitative descriptive) grounded in understanding and describing the complexity of views and subjective meanings empirically observed (specifically on a single theme which arises in the case studies: genomic sovereignty)\(^3\). The research is interdisciplinary and is not hypothesis driven in the traditional sense. Instead it is designed to be inductive and exploratory and aims to contribute to preliminary frameworks on large-scale human genomics research in the developing world, which can be validated through subsequent research. Accordingly, the research described here does not rely on a theoretical framework. Instead, qualitative description, as described by Sandelowski (2000)\(^3\) has formed the main basis of inquiry for this dissertation. Qualitative description is an ideal choice as it incorporates naturalistic inquiry and there is no pre-commitment to a theoretical view of the phenomenon under study\(^3\). Moreover, as an approach, it lends itself to “obtaining straight and largely unadorned answer to questions of special relevance to practitioners and policy makers”\(^3\); an overall goal of the research described here.

The logic behind my choosing qualitative description is based upon the fact that at the outset, as represented by the literature review, there was significant literature and analysis on large-scale human genomic variation studies in the developed world from various perspectives. That is not the case, however for the developing world. These developed country analyses have contributed to the development of national legislation and international guidelines and recommendations for large-scale human genomic research and genetic databases. While there has been significant debate for why developing countries should invest in genomics, there have been few empirical
analyses describing why and how these countries are doing so. Thus, little is known with respect to how the evolving trends in large-scale human genomic sciences in the developed world are represented in the developing world. The research described here is designed to be exploratory, employing case study analysis, to enable the necessary flexibility in the research to allow the salient themes to emerge, and permit an open exploration of these themes. It relies on analyzing the emerging trends in the field of human genomic variation studies, identified in the literature review, which form the basis of explanatory case study analyses to meet the research objectives. These objectives are to understand the motivations for proposing and undertaking large-scale genotyping projects; understand the mechanisms that developing countries are envisioning or implementing to develop genomic medicine appropriate to their own circumstances; explore the potential for commercialization of the results of such projects; understand the challenges faced and how those challenges are being resolved; and to investigate the emerging potential, ethical, legal, social issues that have arisen or might arise as a result of these projects.

Larger paradigms can influence the design of qualitative description. Here key influences include, the national innovation system theory, which can facilitate understanding of the adoption and implementation of science and technology in developing countries. The research questions are influenced by innovation system theory to guide data collection and analysis, specifically to recognize that diverse actors are involved in promoting new developments in developing countries and focusing on their interactions is important. This was particularly useful to identify several appropriate stakeholders. As described by Thorsteinsdottir and colleagues (2004), the health biotechnology innovation system in developing countries is made up of the actors, institutions (research and development, financial and educational),
organizations and policies that together support the adoption of- and implementation of health biotechnology. In the case of the research described here, the health biotechnology is genomics and genome-based technologies (specifically large-scale human genomic variation initiatives), which in the short term are focused upon basic health research, but in the long term are anticipated to generate health-based innovation, in the form of genomic medicine.

3.3 Research Design

Case Study Research

Qualitative case study methods were used for this research. Case studies are appropriate for studying these large-scale genotyping projects, as they are ideal for generating rich description within a specific context. As a strategy of inquiry, case studies enable the in-depth exploration of real-life phenomenon within a fixed time frame and bounded activity where there is little known, little empirical substantiation, the need for a new perspective, and potentially a conflict in ideas. These are all features of the larger research question being asked here of ‘how and why do developing countries engage in locally led, large-scale genotyping projects’. In addition, as a method, the case study can accommodate multiple variables of interest and sources of evidence, a specific feature of the research described here, to guide data collection and analysis. According to Yin (2009), it is essential to clearly define the case and unit of analysis in order to assess the limits of the data collection.

Chapters 4 and 5 present two descriptive case study analyses, which I led and that have already been peer-reviewed and published by Nature Reviews Genetics. The first case study is a large-scale genotyping project documenting human genomic variation in India and the second case
study is a proposed project in South Africa. In the face of several challenges the South Africa project did not proceed, however the case study provided an opportunity to study an outlier and learn more about challenges faced by developing countries.

**The Indian Genome Variation database (IGVdb) Consortium in India**

The IGVdb was initiated by six academic institutes of the Council of Scientific Industrial Research (CSIR) and is funded by the Government of India. The IGVdb aims to create a DNA variation database of the people of India and make it available to researchers for understanding human biology with respect to disease predisposition, adverse drug reaction, population migration etc. They will sample 15,000 unrelated individuals of different sub-populations on the basis of geography and linguistics and will focus upon 72 disease genes, thought to be common in the Indian population\(^1\).

**University of Cape Town’s (UCT) Division of Human Genetics/The Africa Genome Education Institute (AGEI) (South Africa)**

The Division of Human Genetics at UCT is currently involved in several projects including, elucidating the genetic basis of diseases in South Africa and exploring ancestry in indigenous populations in South Africa [http://web.uct.ac.za/depts/genetics]. The AGEI is devoted to educating the public about the structure and function of genomes as well as studying the genetic basis of diseases relevant to the South African population. Although there have been efforts to launch a national large-scale genotyping initiative exploring human genomic diversity in both indigenous and immigrant populations in South Africa, it has not yet been implemented. As a result, this case study will focus upon the existing landscape in South Africa: a) current human genotyping studies, pharmacogenomic/pharmacogenetics studies and disease-association studies b) challenges and barriers to implementing such an initiative c) potential benefits and implications of said initiative\(^3\).
As part of a larger project, *Human Genomic Variation: Implications for Global Health* (already described, see page 5), I also collaborated on additional case studies in Mexico and Thailand as well as on the HUGO Pan Asia Consortium (see Appendix 1 for the resulting publications on which I am a co-author). Although these case studies do not constitute a formal part of my thesis, I was a major contributor to these publications and the data generated from these papers informed this thesis. I have collaborated on a cross-comparative analysis of these case studies that has resulted in a peer-reviewed publication featured in *Nature Reviews Genetics* (see Appendix 1 for the publication). The data from this cross-comparison analysis also informs both Chapters 6 and 7. These case studies are as follows:

**The Mexican Institute for Genomic Medicine (INMEGEN):**

INMEGEN was created by the Mexican Ministry of Health (SSA), the National Autonomous University of Mexico (UNAM), the Mexican Health Foundation (FUNSALUD), and the National Council of Science and Technology. The project will involve sampling individuals from six regions in Mexico in order to produce a clear picture of the genetic variation associated with the Mexican population and is the largest genotyping of its kind in Latin America. The information will be used to improve the health of the Mexican population through its application to local health problems as well as those of other countries with large mestizo populations.14,17 (Also see: [http://www.inmegen.org.mx](http://www.inmegen.org.mx)).

**The Thai SNP Discovery Project and the Thai Center for Excellence in Life Sciences Pharmacogenomic Project**

The Thai SNP Discovery Project [http://thaisnp.biotec.or.th/] and is a collaborative effort between Mahidol University’s Faculty of Medicine, Ramathibodi Hospital and Oracle Co. Ltd.
(Thailand), the National Center for Genetic Engineering and Biotechnology (BIOTEC, Thailand) and Centre National de Génotypage (CNG, France). A SNP database will contain allele frequency and linkage disequilibrium (LD) block patterns for all genes identified in the human genome and their regulatory regions in Thai and other (French, Japanese and African) populations. The database will also contain other information such as genomic sequences, genomic structure, primer sequences and functional genomic information. The information from this database will be used to identify disease-associated genes, for the candidate gene approach and systematic genome screening as well as for pharmacogenomic research. It will also form the Thai contribution to the HUGO Pan Asian SNP consortium. The Thailand Centre of Excellence in Life Sciences (TCELS) Pharmacogenomics Project [http://www.tcels.or.th/en/ProjectsDetail.asp?projectID=60] has performed SNP genotyping of genes involved in drug response. They are also collaborating with the RIKEN institute in Japan, which has collected 3000 samples of patients suffering from post-traumatic stress disorder in order to understand any genomic contributions to this syndrome. Other disease areas that will be investigated by the TCELS pharmacogenomics project include diabetes, cardiovascular diseases, rheumatoid arthritis, HIV/AIDS, lupus, childhood leukemia and DPD deficiency.

The HUGO Pacific Pan-Asian SNP Initiative

The HUGO Pacific Pan-Asian SNP Initiative is a collaborative effort between scientists from China, India, Indonesia, Japan, Korea, Malaysia, Nepal, Philippines, Singapore, Thailand and Taiwan who are studying the genetic diversity in Asian populations. The results from the study will be made available to the public. The goal of this initiative is to uncover the breadth of genetic diversity and the extent of genetic similarity in Asia’. It is further hoped that this information, in the future, will enable researchers to determine why certain subpopulations do not respond to certain drug therapies or are more susceptible to specific diseases.
Unit of case study analysis

The unit of analysis is the described large-scale genotyping project for each of these case studies. The timeframe of data collection began in 2006 with the approval of the Human Genomic Variation: Implications for Global Health project and ceased at the end of field research in 2009. Large-scale genotyping projects, as defined earlier, involve several stages, including the collection of samples (blood, saliva or tissue or combinations thereof), which are subsequently typed (assayed for allelic variation). The samples may or may not be stored along with the genotype data in a genomic database. These databases provide baseline information on single nucleotide polymorphisms (SNPs) and in some cases, copy number variation (CNVs) within the local population. The research was conducted through institutional affiliations with the Division of Human Genetics at UCT in South Africa and with the Institute of Genomics and Integrative Biology (IGIB), Council of Scientific and Industrial Research (CSIR), India. These affiliations ensured that ethical considerations in each country were appropriately addressed and helped to identify the necessary material and facilitate key-informants for interview.

Justification and selection of the cases

The cases themselves were selected, as part of a larger project Human Genomic Variation: Implications for Global Health, for three specific reasons. First, to our knowledge, these projects were the most advanced locally driven projects with respect to planning or implementation; second, the countries the initiatives were housed in provided a good regional representation of the developing world; and third, access to key informants was facilitated by pre-existing contacts with individuals involved in these initiatives, thereby enabling necessary collaboration.
3.4 Data Collection and Analysis

Data Collection

The data set for each case study has been and is collected from two primary sources: publicly available relevant documents and interviews with key informants.

Participant selection and recruitment

In each of the case studies, key informants were identified and contacted by email or telephone through a mixture of purposeful and snowball sampling\textsuperscript{330,331,341}. The sample size was undetermined; and data collection essentially ceased when thematic data saturation occurred and incremental improvement to the themes became minimal\textsuperscript{341}. Informants included those involved in the initial conceptual stages of the projects as well as those who were involved with the successful (or unsuccessful) implementation of the projects. Subsequent key informants were selected as recommended by those initial informants. Additionally, in an effort to identify individuals that would be important to the implementation of human genomic variation studies and adoption genomic medicine generally, the innovation system theory, as it applies to developing countries\textsuperscript{335} was used.

Semi-structured Interviews

Semi-structured, face-to-face and teleconference interviews (see Appendix 3 for the interview guides for South Africa and India) were the main source of data collection for these case studies. This approach enables access to historical information through participants and greater control over the line of questioning\textsuperscript{330}. Participants were asked questions about the motivations behind conducting- and the implications of- human genomic diversity studies, as well as the opportunities associated with such research and how to best leverage the findings
within their respective countries. As is typical in qualitative case studies, the interview guide was modified during data analysis to capitalize on emerging themes. I emphasized different aspects of the interview guide depending on the background of the interviewee, and tailored the questions accordingly – often thematically. As I modified the interview guides, I sent a copy of the revised questionnaire versions to the research ethics board. The interviews are digitally recorded and transcribed and lasted approximately 30 minutes to 1.5 hour. The interviews took place at the institutions of the informants, making it possible to augment the collection of information by observing their facilities. In the rare case, where this was not possible, interviews were conducted by teleconference. The breakdown of the interviews is as follows:

In India, 17 interviews were conducted with 15 key informants, representing scientists and managers at the IGVdb and key informants from diverse backgrounds, such as regulatory and government officials, one policy analyst, and experts in the area of genomics/pharmacogenomics and bioethicists from developed and developing countries, to understand the motivation for- and the process behind the successful initiative.

In South Africa, 21 interviews were conducted with 21 key informants, representing members of the African Genome Education Institute (AGEI) and the Division of Human genetics at UCT as well as key informants from diverse backgrounds, including institutional research units, government officials, funding agencies, and experts in the area of genomics/pharmacogenomics and bioethicists from developed and developing countries, to understand the motivation for- and the process behind the failed initiative.

Documents
Concurrent with key-informant interviews, documents were collected and analyzed. Document collection can provide the researcher with an unobtrusive source of data, which can enrich the transcripts obtained from the interviewing process\(^{330}\). The documents collected include all publicly available materials relevant to the study questions. And examples include: newspapers articles, peer-reviewed publications and publication drafts, ethics protocols, informed consent sheets, government and institutional reports, white papers, patent legislation, health legislation, national drug policies, science and technology policies, press releases, and so on. From these documents, data on involved participants, policy contexts and processes as they related to the units of analyses were identified.

**Data Analysis**

These are qualitative case studies employing thematic network analysis\(^ {342}\) and consisted of three steps as described by Strauss and Corbin (1998)\(^ {343}\). Transcripts were transcribed and analyzed using ATLAS.ti software. Theme categories were identified by analyzing the interview transcripts by generative or open coding; that is, analysis of words repetitions, key terms and key words. The next phase of data analysis consisted of axial coding of the data, which allowed us to build connections within and between theme categories. In the final phase I identified core concepts by using selective coding. Field notes and observations generated during the interviews and throughout the study (for example at various symposia and conferences) were also analyzed and relevant documents, including informed consent sheets, ethics protocols, publications etc., were gathered during the interviews and reviewed.

**Validity and limitations of the Research Methods**
The issue of validity was addressed in three ways, as described by Creswell (2009)\(^3\). First, different data sources (e.g. documents, literature and interviews, field notes and observations) were triangulated; when different perspectives converged on similar themes it helped to justify the themes. Second, debriefings on codes and themes with other members of my team, on the larger project *Human genomic variation implications for global health*, and my supervisor, were held to ensure accuracy of specific descriptions and limit researcher bias. Third, in many instances, not all, member checking was conducted and where possible, feedback was incorporated. For instance, for Chapters 4 and 5, member checking was conducted prior to publication. In addition, for Chapter 6, while in the field, I have held extensive discussions post-interview with a handful of key informants who have spoken or published on the issue of genomic sovereignty in an effort to gain feedback on the qualitative themes as they were being developed.

Some of the limitations of these research methods include: interviewee and interviewer bias, limited observation on the part of the researcher, researcher-interviewee dynamic (establishing trust, etc.) and the potential lack of expertise among participants\(^3\). For instance, as an outsider, it was difficult for me to tease out all of the relevant contextual aspects during the interview process. Interviewees may have been biased and were not always forthcoming, and at times requested that we speak ‘off the record’; there is an interest in science and technology in the developing world to promote the positive. I attempted to mitigate this issue, when possible, by locating and interviewing detractors and attempted to locate negative views in the literature. However, those individuals were often not willing to go ‘on record’. Oftentimes documents and literature were not available or limited due to lack of infrastructure or poor governance, reducing the effectiveness of triangulation. Documents were also limited in that they may have been biased, inaccurate, inauthentic and incomplete\(^3\). Moreover case study observations were
limited by the time dedicated to fieldwork (approximately 2-3 weeks); with a significant amount of time spent acclimatizing to the environments. I also was not able to access certain stakeholders. For instance, in South Africa, some members of the government expressed ‘study exhaustion’ and would decline interviews. Finally the strength of case studies is that they are able to bound a phenomenon in time. However, this can also be a weakness. The field of human genomic variation is rapidly evolving, thus the opinions expressed by the participants may no longer be relevant or representative.

3.5 Ethical Considerations

Each case study proceeded only after ethics approval had been obtained from the University of Toronto Research Ethics Board. Written free and informed consent was obtained from each participant before the interviews proceeded and after the details of the study and the nature of participation had been carefully explained (See Appendix 4 for the Study Information and Consent Form). All digital files and transcripts are kept on a secure, password-protected computer with restricted access. All field notes are stored in a locked cabinet at the McLaughlin-Rotman Centre for Global Health. The confidentiality of the information was discussed with the key informants. They will only be listed as key informants with their consent.
Chapter 4
From diversity to delivery: the case of the Indian Genome Variation initiative

4

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As lead author, I was responsible for conducting the interviews, analyzing the data and developing the concepts and themes, as well as writing the paper. Listed co-authors contributed to the initial conceptualization of the project, facilitating access to participants as well as providing essential comments throughout the drafting of the publication.

4.1 Introduction

India currently has the world’s second-largest population along with a fast-growing economy and significant economic disparity. It also continues to experience a high rate of infectious disease and increasingly higher rates of chronic diseases. However, India cannot afford to import expensive technologies and therapeutics nor can it, as an emerging economy, emulate the health-delivery systems of the developed world. Instead, to address these challenges it is looking to biotechnology-based innovation in the field of genomics. The Indian Genome Variation (IGV) consortium, a government-funded collaborative network among seven local institutions, is a reflection of these efforts. The IGV has recently developed the first large-scale database of genomic diversity in the Indian population that will facilitate research on disease predisposition, adverse drug reactions and population migration.
4.2 Background

With one of the world’s largest populations, a high burden of infectious disease and an increasing rate of chronic disease, India cannot afford to adopt existing and expensive Western health-care models to address its local health needs. Instead India needs to look to innovative, cost effective models, including adopting emerging health technologies. Genomic sciences and related technologies can add value to India’s local health-care system by emphasizing prediction and prevention, and possibly decreasing the cost of health care through better diagnosis, early detection, and improved treatment and management. Moreover, by investing in these emerging genomic health product innovation system, building capacity in science and technology (S&T) to provide it with a competitive edge in the knowledge-based economy, resulting in economic stimulation. Here we present our findings on a case study of the India Genome Variation (IGV) database, a collaborative network initiative that recognized both the richness and the significance of human genomic diversity within the Indian population, as well as the need for a pan Indian data resource. The resulting database captures essential data about disease predisposition, adverse drug reactions (ADRs) and population migration within India.

The IGV is a collaboration between the Council of Scientific and Industrial Research (CSIR) institutes, the Institute of Genomics and Integrative Biology (IGIB), the Centre for Cellular and Molecular Biology, the Indian Institute of Chemical Biology, the Central Drug Research Institute, the Industrial Toxicological Research Centre, the Institute of Microbial Technology and the Indian Statistical Institute (ISI), Kolkata. The IGV data bank contains samples from up to 15,000 unrelated individuals from various subpopulations in India, on the basis of their different geographical zone (northern, southern, eastern, western, central and north-eastern) and linguistic
categories (Tibeto-Burman, Dravidian, Indo-European and Austro-Asiatic). Using previously described qualitative methods, we performed 15 in-depth semi-structured interviews with 17 key informants representing scientists and managers at the IGV and key informants with from diverse backgrounds, such as regulatory and government officials, one policy analyst, and experts in the areas of genomics/Pharmacogenetics and ethics from developed and developing countries, to understand the motivation for and the process behind the creation of an initiative such as the IGV database.

4.3 Adoption of Genomic Medicine in India

4.3.1 Knowledge-based economy

Economic benefits were a key driver behind the creation of the IGV – a reflection of the Indian government’s broader attempt to support economic development through investment in S&T-based innovation. Participants explained to us that emerging innovative genomic-based initiatives such as the IGV contribute towards scientific capacity building, developing and retaining valuable human resources, and providing Indian scientists and the growing domestic private sector with a competitive edge on the global market. In a step towards this last goal, members of the IGV have proposed developing a predictive population therapy database. The database, either solely using IGV data or potentially in combination with additional clinical data would enable various clients to select clinical trial participants in order to stratify clinical trials. Multinationals have been increasingly conducting early stage clinical trials in India because of the cost savings and the readily accessible, largely drug-naïve population resource. India has thus positioned itself as a global hub for conducting clinical trial research by investing in capacity and infrastructure. Some domestic companies subsidize their research and development (R&D) platforms by providing contract services for clinical trials to multinational
and foreign companies\textsuperscript{349}. Accordingly, a ‘predictive population database’ could help maintain India’s competitive edge by improving the selection specificity through stratification of the test population, thereby further reducing the time and cost associated with conducting clinical trials in India.

Members of the IGV are also exploring innovative applications in niche markets. For instance, a new field, termed Ayurgenomics, is investigating the potential relationship between human genomic variation, pharmacogenomics, personalized therapeutics and the traditional medicine Ayurveda. Individual variation was described in India by Chakara over 4,000 years ago and it continues to be the basic principle of the Ayurveda, which is still widely practiced across India\textsuperscript{350,351}.

The IGV also hopes to contribute to the Indian biotechnology sector, which experienced a growth rate of 30\% in 2007 led by the bio-pharma sector\textsuperscript{352}. For instance, it is making efforts to protect its basic research discoveries. Currently, the IGV provides the global academic community with access to its database through an internet portal under a click wrap agreement (an online agreement prompting users to read and agree to the terms of use prior to access). We were told by participants, however, that the discoveries made by IGV will be protected through patents and will subsequently need to be licensed through the IGV. The IGV has also begun to provide its researchers with commercialization support in order to encourage translation of basic research to potential products and therapeutics. It has partnered with a not-for-profit, public-private technology-transfer laboratory – The Centre for Genomic Applications (TCGA). The TCGA is a partnership between the Institute for Molecular Medicine, the IGIB, the Council for Scientific and Industrial Research (CSIR) and the Chatterjee Group. The TCGA, in partnership with IGV researchers, will provide the technological expertise and capacity to conduct the proof
of concept and Phase I clinical studies that are needed to encourage domestic and foreign industry investment into early stage commercial opportunities in India.

The development of therapeutic products or services from the IGV database is unlikely in the near future, given its early stage of development. Thus, in terms of more immediate commercialization opportunities from human genomic diversity knowledge, we tried to gauge the involvement of the domestic private sector. Generally, we found it to be limited; however, Avesthagen Ltd, an Indian life-sciences company, announced in March 2007 that it will be initiating a large-scale genotyping project of the Parsi population – the Avesthagenome project. Estimated to take up to 5 years to complete and costing approximately US$32 million, the project proposes to genotype India’s entire Parsi population (~69,000 people) and develop a database containing genomic information as well as linkage to family history and medical records. The Parsis are an ethnic minority in India who are considered genetically homogenous and are feared to be at risk of extinction owing to their religion, which prohibits marriages outside of the community. The aim is to determine the link between genes, disease and environmental factors to better understand disease and to develop new therapies and diagnostics with a focus on chronic diseases, such as cancer and central nervous system disorders, that can be used to directly benefit the Parsi population, with an additional potential to be marketed globally where appropriate.

The IGV is looking to position the Indian research community as a global knowledge partner, as opposed to a service provider that facilitates foreign research. Crucial to their success are their exploration of niche market opportunities (for example, Ayurgenomics), their efforts to encourage patent protection of research discoveries and the establishment of strategic partnerships to foster the translation of basic research. In addition to these approaches, the IGV
needs to consider mechanisms to provide support to researchers wishing to out-license or create companies on the basis of their technology. They will also need to further pursue strategic opportunities with the domestic private sector. For instance, how can the complementarities between the IGV and the Avesthagenome project be best leveraged? Until much of the IGV data is validated the existing initiatives will provide the consortium with the momentum required to get started.

4.3.2 Genomic Sovereignty

Key informants in several developing countries have told us that in order to generate the potential health and economic benefits expected from human genomic diversity studies, they will need to prevent unapproved exports of genomic materials and protect the data contained therein through legislation. India is no exception. One fifth of the global population lives in India and thus a significant amount of human genomic variation can be found there. Accordingly, key informants in this study asserted that the availability of India’s large population resource, with its multi-generational endogamous families and well maintained genealogical records, provides them with a unique research advantage. Participants advised us that, in the past, Indian physicians were provided with incentives (for example, vacations and/or equipment) by foreign researchers in order to encourage them to share their patient samples. These physicians were often not aware that by doing so they might inadvertently be contributing to foreign patents on discoveries made using Indian patient samples that would subsequently limit local access to resulting therapeutics. Many of the participants we interviewed also cited repeated conflicts between sharing and publications. Thus, in November 1997, the Guidelines for Exchange of Human Biological Material for Biomedical Research Purposes were updated by the Indian Council of Medical Research (ICMR) so that government permission is required for the export, these guidelines have provided Indian researchers with a mechanism to protect their discoveries.
However, several participants pointed out that these guidelines are not enforceable owing to a lack of human resources. Moreover, multinational pharmaceutical companies conducting research within India are able to bypass these guidelines and, although they might be providing training and employment, there are no guarantees that the Indian population will gain significant long-term economic or health benefits from this research. Interviewees thus recommended that the Indian government establish legislation to enforce the guidelines and extend them to address the collection and use of genomic data by multinationals conducting research within the country. However, if the Indian government were to establish genomic sovereignty legislation, such as that recently enacted in Mexico, it is not clear how it would be enforced. Moreover, recent concerns have arisen regarding biodiversity legislation in India – in its current form it impedes international collaboration, reducing opportunities for Indian scientists to share their data and contribute to larger research projects. The debate is an important one, as the knowledge generated from these national data banks might need to be interpreted in larger international collaborative efforts before it can contribute to generating practical health benefits.

4.3.3 Political Will

In 2001, the Indian Ministry of Health pledged $20 million in public funding towards medical genomics. Consequently, in addition to the IGV, which received $5 million from the CSIR, there are several genotyping and genomic-based research initiatives that receive public funding for basic research from the ICMR, the Department of Biotechnology (DBT) and the CSIR. Moreover, in 2007, the Indian government approved the National Biotechnology Strategy (also known as the Strategy), a policy document prepared by the DBT. The DBT falls under the Ministry of Science and Technology, and is linked with the commercial development of biology and biotechnology in India. The Strategy outlines proposed actions for boosting the translation of life-sciences knowledge, such as creating investment capital, boosting technology
transfer and intellectual property regulations, addressing regulatory issues and enhancing public understanding. Earlier drafts of the Strategy also highlighted genomic medicine as a strategic direction and proposed that India could act as a global hub for genomic medicine R&D. In addition to strategic policy, ethical guidelines for bio-banking in India have been established by the ICMR (see: http://www.icmr.nic.in/ethical_guideliens.pdf). These types of guidelines can stimulate R&D because they provide a framework with parameters that scientists and industry can work within, while also ensuring transparency and public accountability. In order to ensure that the research generated by the IGV is leveraged towards economic and health benefits, it is crucial that the political will in place now is maintained and that basic research is supported throughout development, commercialization and delivery. The approval of these strategies and guidelines provides the momentum necessary to do so. However, the Indian government will need to develop success measures for the Strategy and focus on developing future policy guidelines for regulatory and delivery issues to ensure public acceptance. For instance, it is thought that the Genetic Information Non-Discrimination Act (GINA), recently passed by the United States (US) Congress, will help spur public acceptance of the genomic medicine industry in the US.

4.3.4 Local Health Benefits

India has a history of investing in genetic research to improve local health. Key informants told us that genetic research in India has resulted in tangible public health benefits, such as blood banks and screening registries. For instance, the DBT has established 16 units throughout India that provide genetic diagnosis and genetic counseling services for prenatal diagnosis and genetic disorders, such as beta-thalassaemia, Duchenne Muscular Dystrophy, haemoglobinopathies and neurogenetic disorders, that are prevalent in the country (see The Human Genome and Human Genetics at:}
We were told that genetic research in India has resulted in social benefits, such as reduced stigmatization previously associated with genetic disease. Accordingly, the IGV has been publicly funded with the expectation that, in the long term, it will promote local health savings through advances in understanding predisposition to disease, mechanisms of disease, pharmacogenomics and personalized medicine. Members of the IGV have recently published their results on 405 SNPs in 75 disease genes and a 5.2 Mb region of chromosome 22 in 1,871 individuals from 55 population groups in India. Using these SNPs, members of IGV are currently conducting population-based screens for susceptibility to asthma, diabetes, neuropsychiatric disorders, high-altitude sickness, retinitis pigmentosa, malaria and infectious diseases as well as variation in drug metabolism.

Members of the IGV also told us of an application they are developing that might reduce healthcare cost in India – a predictive population therapy database that investigates drug response variability in the Indian population. One participant provided the basis for why a database could be beneficial when he told us that: “[up to] 13% of the Indian population does not respond to up to 30 very essential drugs in Northern India…”. As a result, low cost therapeutics for which there are high rates of non-response and ADRs are often substituted for by newer, more expensive therapeutics. If the non-responder and ADR cases can be explained by genomic variation, these expensive substitutions can be superseded with better tailored treatments. As a proof of concept, researchers at the IGV have demonstrated an association between a panel of SNPs located at the beta(2)-adrenergic receptor (β2AR) locus and the response to salbutamol, a low-cost asthma therapeutic, in Indian asthma patients. These results could be used to design a diagnostic that would identify patients that are resistant to salbutamol. Although this method can
contribute to reducing individual health-care costs and ultimately contribute to improving public health, given the size of India’s population and disparate levels of education and poverty across the country there are significant challenges in ensuring the adoption and delivery of the benefits associated with genomic medicine. For instance, in contrast to the National Institute of Genomic Medicine (INMEGEN) in Mexico\textsuperscript{362}, the IGV is not linked with the Indian Ministry of Health, creating a gap between R&D and the eventual delivery of local health benefits.

4.4 Genomic Medicine Challenges in India

4.4.1 Academic links

Strong links and synergies between institutions provide opportunities for knowledge flow and the development of expertise and are part of a successful health biotechnology innovation system\textsuperscript{363}. The IGV is a unique example in this regard and has set the trend for many new consortia initiatives in India. Nevertheless, according to our key informants, coordination between academic institutions in India remains weak. One government official pointed out how this lack of coordination can result in barriers to progress and can prevent industry involvement. Consequently, public research institutions in India need to develop a national foresight map for large-scale genotyping projects, human genomic variation studies and disease association studies that will help leverage existing data networks and create opportunities for collaboration between institutions.

4.4.2 Public-private sector links

Local private-sector involvement, to develop and commercialize knowledge, is necessary for sustainable development in a country’s health-related biotechnology sector\textsuperscript{363,364}. Although partnerships between academic institutions and industry continue to strengthen in India, to date they remain insubstantial\textsuperscript{349}. Policy efforts exist to promote these partnerships. For instance, the
CSIR provides public-private partnership grants (see: New Millennium India Technology Leadership Initiative\textsuperscript{365}). In addition, the National Biotechnology Development Strategy recently proposed increased spending on public-private partnerships initiatives and a Biotechnology Industry Partnership Program for Advanced Technologies. Although these programmes are a good start, their robustness remains to be tested. Key informants told us that data sharing often created a barrier to these partnerships; negotiations regarding data sharing can be affected by disagreements over publication timelines, intellectual property rights and return on investment strategies. Moreover, our informants maintained that the local private sector is either uninterested or not prepared to foray into genomic medicine; partly owing to their interest in short-term gain and financial restraints as well as their lack of R&D capacity. However, the announcement of Avesthagenome might signal a burgeoning interest by the domestic private sector.

4.4.3 Commercialization in the public sector

Commercialization of research associated with the IGV, as well as other Indian institutions involved in human genomic variation studies, is generally seen as a long-term goal. Researchers point out that human genomic variation studies are in their early stages, require further validation and currently have few obvious commercial applications. As a result, Indian researchers generally view peer-reviewed publications as a more important goal than research commercialization. Perhaps reflecting this lack of interest in commercialization, we were told that some institutions are currently providing local clinics with their findings on drug response variation to enable physicians to account for these differences when treating their patients. Some members of the IGV have addressed this challenge by entering into a partnership with the TCGA, thereby ensuring that commercialization of basic research is encouraged. However, additional incentives, such as the proposals made in the recent National Biotechnology
Development Strategy, will also need to be implemented if India is to become a hub for R&D in genomic medicine.

4.4.4 The need for regulatory frameworks

The Indian Ministry of Health regulates all drugs and related products as well as clinical trials in collaboration with the ICMR and the DBT, through the Central Drugs Standard Control Organization (CDSCO). The CDSCO has not yet established guidelines for clinical trials or therapeutics that rely on population differences, genomic sciences, population-based therapeutics or pharmacogenomics. We were told by a regulatory official that regulations were not necessary as there were no available products as yet. Instead, he suggested that the regulatory framework will evolve as these products become available. By contrast, researchers felt that the lack of regulatory guidelines in India will serve as a barrier to the adoption of genomic sciences for health benefits because there is no incentive to report clinical data or develop products. Key informants recommended that imported therapeutics that show population variance in their efficacy should undergo clinical trials in India prior to approval, and that all clinical trials should submit genomic variation data. For instance, one participant mentioned that: “a lot of vaccine trials are going to happen in India in the near future; [it would be] very important to look at the pharmacogenomics of that.” But even if the CDSCO were to implement guidelines, voluntary or otherwise, the resources needed to initiate and monitor adherence to regulatory guidelines are not in place. As one interviewee pointed out: “Indian systems are very proactive today. They really want to do things. So the leadership is very clear. But what the leadership is lacking are people under them.”
4.4.5 Delivery requires innovative solutions

It has been suggested that the benefits of genomic medicine will not reach the poor owing to the expected high cost of delivery\(^7\). 34% of India’s population continues to exist on less that $1 per day (see India Country Overview 2007\(^{366}\) from the World Bank web site). Moreover, there is significant inequality between the rural and urban regions, with approximately 72.2% of India’s population living in rural areas (see the Census of India Rural-Urban Distribution\(^{367}\)). The suggestion that these rural poor make India a potentially poor market for genomic medicine is now being challenged by models that suggest that these populations are more receptive to innovative technologies. Indeed, the rural poor are thought to make up part of a potentially multitrillion dollar market, with suggestions that their informal economy accounts for 40-60% of the economic activity in the developing world\(^{368}\). These lessons are directly applicable in India. For example, we learned of a partnership being negotiated between a private company and an Indian bank for a rural model for delivery, through micro-franchising, of functional foods (processed foods with added nutritional claims of health promotion and/or disease prevention) and nutriceuticals. In the long term, similar delivery models could be extended to genomic medicine: cheap diagnostics could be provided at the level of the village to identify those patients who would need to travel to the urban regions for treatment. Large health-care units, banks and industry could develop partnerships to cut costs of treatment and improve their ability to harness this market by tapping into the existing infrastructure. Clearly, genomic medicine is in its early stages and cheap diagnostics have yet to be developed. However, if local health benefits are expected to reach the whole population, it is appropriate to begin examining models of how to best harness these markets. In order to move such proposals forward, stakeholders will need to address the concerns associated with the involvement of the private sector, insurance providers and banks in the delivery of health care.
4.4.6 Physicians’ understanding

Physicians’ understanding of genomic medicine and its applications is limited in India. Consequently, integration of genomic medicine in the clinic will pose a challenge. Physicians will require instruction on human genomic variation and how to use this variation for the benefit of medical practice, including how drug efficacy and safety can be affected by common genetic polymorphisms in drug-metabolizing enzymes. However, as one researcher said: “…our medical curricula don’t have structure for pharmacogenomics or for understanding how genetics would be applied to medicine.” In an effort to bridge this gap between research and physicians, we were told of non-governmental physician education programmes, such as the Moving Academy of Medicine and the government website Genetics India, which provide information on the use of genetics in medicine. Moreover, institutes such as the Manipal Life Sciences Centre at Manipal University provide presentations on genomics and potential applications to doctors. However, for effective physician education to take place, standardized programmes on genomics and genomic-based applications will need to be implemented within the medical curricula at universities, such as those that are being implemented by INMEGEN 362.

4.4.7 Public Awareness

Public awareness of human genomic variation, genotyping initiatives and genomic medicine in India remains unclear. The informants we interviewed stated that public awareness of these subjects was low because of the lack of public engagement. One interviewee pointed out that scientists and researchers rarely engage with the public on scientific issues because “…we have problems in our country with respect to how much information you would divulge because of […] the status of education.” Even so, there is evidence of non-governmental organizations spear-heading efforts to inform the public on medical biotechnology and its potential applications. The Jan Swasthya Abhiyan group, a national coordination committee, distributes a
pamphlet entitled ‘New Technologies in Public Health – Who Pays and Who Benefits?’ that provides the general public with the People’s Health Movement views on the ethical and social implications of genomics and health.

However, some participants felt that because of the public’s familiarity with Ayurveda, a traditional form of personalized medicine, extending the personalized approach to include genomics would meet with little resistance. One interviewee told us: “of course that is something very different about the way we look at pharmacogenomics and the genotyping and the phenotyping correlation. But that concept had existed.” But the interviewees were clear that without the support of the public the adoption of genomic medicine in to the health-care setting will be difficult. Thus, interviewees recommended that development and implementation of public engagement programmes to increase public awareness and understanding and to increase public support.

4.5 Concluding Remarks

India is spearheading efforts to benefit from genotyping projects and associated technologies, including pharmacogenomic and genome-wide disease association studies. Here, we documented this trajectory by exploring the IGV. The IGV is a reflection of the desire to fuel economic development through investment in S&T innovation, the belief that there will be significant public health benefits and savings to the health-care system, and the need to ensure that genomic variation contained within the Indian population is harnessed to its benefit. The IGV was initiated, despite limited resources, by instituting a vertically integrated network of existing research institutions and public-private partnerships with service providers. The IGV is currently validating its data and, given its early stage of development, whether it meets any of its long-term goals remains to be seen.
Before the IGV can become a sustainable initiative with concrete benefits, such as health applications derived from the knowledge of genomic variation, there are a number of challenges that will need to be addressed within the Indian life-sciences innovation framework. In some cases, the IGV and the DBT have addressed these challenges, as exemplified by the IGV partnership with TCGA and the DBT’s Biotechnology Strategy that address challenges to commercialization and collaboration. However, in the area of regulatory guidelines, physician understanding and public engagement, there has been little or no activity. These important challenges need to be addressed in the near future as other genotyping and pharmacogenomic initiatives are underway in India, both in the private and public sector. A few of these challenges are being effectively addressed in Mexico (INMEGEN)\textsuperscript{362}, South Africa (African Genome Education Institute)\textsuperscript{338} and Thailand (Thailand Center for Excellence in Life Sciences)\textsuperscript{339} to which India could look for guidance; others are being experienced internationally, providing India with the opportunity to develop innovative solutions and become a global leader in this sector.
Chapter 5
South Africa: from species cradle to genomic applications

5

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As lead author, I was responsible for conducting the interviews, analyzing the data and developing the concepts and themes, as well as writing the paper. Listed co-authors contributed to the initial conceptualization of the project, facilitating access to participants as well as providing essential comments throughout the drafting of the publication.

5.1 Introduction

The South African government is committed to science and technology innovation, to establishing a knowledge-based economy and to harnessing life-sciences research for health and economic development. Given the constraints and the early stage of development of the field as a whole in South Africa, we found an impressive amount of research on human genomic variation in this country. Encouragingly, South Africa is beginning to apply genomics to address local health needs, including HIV and tuberculosis (TB) infections. We document a number of initiatives in South Africa that are beginning to study genetic variation within the various local indigenous populations. Other early initiatives focus on pharmacogenetic studies, mutation characterization in individual disease genes and genome-wide association studies. Public engagement in genomic issues is spear-headed by the Africa Genome Education Institute.
5.2 Background

Sub-Saharan Africa, where modern humans arose\textsuperscript{369-371}, is home to a wealth of human diversity\textsuperscript{372}. There is thus much to be learnt from characterizing human genomic variation in this part of Africa, especially with regards to health applications. In recent years, the African Society of Human Genetics (AfSHG) has begun to raise awareness of genomics and genetics in Africa with a focus on networking and capacity building throughout the continent. South Africa in particular has generated new scientific capacity in the field of genomic sciences, including the recently launched high throughput genomics platform at Lifelabs located at the Nelson R. Mandela School of Medicine at the University of KwaZuluNatal, and the Centre for Proteomic and Genomic Research (CPGR) at the University of Cape Town (UCT). These initiatives are in line with the recent report by the African Union High Level Panel on Modern Biotechnology, entitled ‘Freedom to Innovate’ (see: http://www.nepadst.org/doclibrary/pdfs/biotech_africa_2007.pdf, which recommends that Southern Africa focuses on a ‘core mission’ in health biotechnologies while other regions direct biotechnology efforts towards animal health (East Africa), agriculture (West Africa) and forestry (Central Africa).

We have previously described a potential roadmap towards the development of large-scale genotyping projects in emerging economies and the developing world, with examples from Mexico, India and Thailand\textsuperscript{17}. Here we describe a study carried out in South Africa. Using previously described qualitative methods\textsuperscript{17,340} we conducted 21 in-depth semi-structured interviews with members of the African Genome Education Institute (AGEI) and the Division of Human Genetics at UCT as well as key informants from diverse backgrounds, including institutional research units, government officials, funding agencies, genomics/Pharmacogenetics
experts and bioethicists from both developed and developing countries. Where applicable, we present our results using the framework of themes identified in Mexico, India and Thailand: political will, genomic sovereignty, institutional leadership, local health benefits and knowledge-based economy.

5.3 Political Will

We have previously highlighted the value of political will in creating the necessary policy and legislation, public funding and support to encourage the development of genomic medicine in emerging economies and developing nations. For instance, government support through funding and legislation was crucial to the establishment of large-scale genotyping initiatives for health in Mexico, India and Thailand.

In 2001, the National Biotechnology Strategy Report for South Africa, commissioned by the South African government, recommended that the country focus on documenting the genomic diversity contained within the local indigenous and immigrant populations, including: “the mapping and identification of genes underlying disease structure, elucidation of the molecular basis of diseases common to South Africa and the development of technology to develop medicines and diagnostic tests.” The Division of Human genetics at UCT is currently involved in elucidating the genetic basis of diseases (retinal degeneration, hypertension, familial hereditary nonpolyposis colorectal cancer and bipolar disorder) in Southern Africa and exploring genomic diversity in indigenous Southern African populations. In collaboration with the Human Genomic Diversity and Disease Research Unit at the University of the Witwatersrand in Johannesburg, they are characterizing human genomic diversity using biological samples collected from several indigenous tribes in Southern Africa – Zulu, Xhosa, Herero, San and Sotho-Tswana. Although
this study does not look at disease genes *per se*, it will provide data on baseline variation across these populations.

The Division of Human Genetics at UCT has also recently submitted a proposal to the South African government to initiate a national genomic medicine research programme with three components: characterization of human genomic variation within the South African populations, identification of the genomic basis of susceptibility to common diseases (both chronic and infectious) and pharmacogenomics. The research programme will be supported by a national biobank, a high-throughput technology and bioinformatics network, and an economic, education, ethical, legal and social issues (EEELSI) unit. They propose to use this platform to generate research on human genomic variation within the South African population to explore the underlying mechanisms of disease and health as well as for pharmacogenomic and genetics applications. The proposal is currently awaiting approval from government funding agencies.

The 2001 National Biotechnology Strategy has resulted in approximately 450 million South African rand (ZAR) in funding for the development of a biotechnology sector in South Africa. This investment has largely gone towards the establishment of biotechnology regional innovation centres and incubator centres \(^{374-377}\). Key informants highlighted that, although successful, these centres are directed at late-stage research and commercialization. Human genomic variation studies on the other hand, are considered basic research and thus local support for these studies continues to come mainly from traditional government funding agencies, such as the Medical Research Council (MRC), the Department of Science and Technology and the National Research Foundation (NRF), all of which are constrained by how much they can direct into any single research platform project. For instance, the MRC usually provides about 400,000 ZAR (~US$50,00-60,000) per research unit. In some instances, government funding agencies will
match the level of funding for researchers involved in international collaborations that contribute to local capacity building. Thus, key informants felt that despite the infrastructure put in place to serve innovation within the biotechnology sector (including genomics-related research) there remained a gap between policy and action on the part of the South African government. Specifically, there is a lack of available funds to follow up on the above-mentioned 2001 National Biotechnology Strategy recommendations.

It is difficult to predict with the current situation will change given the other pressing priorities faced by the South Africa government. As summarized by one key informant, “I’d like to think that the South African government will come to the party, but then when you look at the nature of other challenges that the country is facing: lack of [electrical] power, need to improve education, need to improve general health-care provision for the general population, need to improve housing provision for the general population…well, where does scientific research fit into all of that? And it is easy for educated scientists who’ve got a vested interest to say, well of course what we are doing is incredibly important and an integral part of all of those challenges for the country.”

The lack of funding for genomics-related research and development (R&D) leads to additional limiting factors, such as the lack of sufficiently trained human resources. Interviewees emphasized their inability to retain locally trained research scientists and attract foreign postdoctoral candidates. They pointed out that they are unable to provide the adequate compensation and the state-of-the-art facilities desired by leaders in the field. In order to address these limitations, South African researchers rely upon international collaborations supported by philanthropic foundations and public institutes, such as the Gates Foundation or the Wellcome Trust, as well as multinational pharmaceutical companies, such as Pfizer and GlaxoSmithKline.
International collaborations form the backbone of many research projects focusing on human genomic variation in South Africa, and all of our key informants considered these partnerships as crucial. However, as a result of these collaborations, key informants also expressed concern that the biological samples, and consequently information, might be leaving the country at a regular pace, potentially affecting the ability of South Africans, and more generally Africans, to capitalize on the results of the associated research.

5.4 Genomic Sovereignty

The concept of genomic sovereignty was previously identified by us as representing a nation’s ability to capture the value of its investments in the field of genomic medicine. In Mexico and India, unique population resources and the desire to prevent exploitation of these resources in part drove the creation of national gene banks. Genomic diversity within sub-Saharan Africa, and for that matter the entire African continent, is relatively under-studied, despite being home to a significant portion of human genomic diversity. South Africa in particular contains a wealth of different population groups. It is home to the indigenous Khoisan, Xhosa, Zulu, Venda, and Sotho Pedi groups, the Afrikaners, and the Coloured, the latter being a uniquely admixed population of immigrant Europeans, Asians and the indigenous populations. Accordingly, all key informants indicated that the South African population, with its rich diversity and multiple isolated populations, is an excellent resource that could provide South African researchers with a unique research advantage. In this context, we were told by participants that South Africa, and Africa generally, also has a long history of ‘parachute research’, whereby foreign scientists obtain human samples from the African continent with no intention of contributing to Africa’s development.
To prevent the parachute research phenomenon the South African government now requires, through the Human tissues Act that individuals exporting biological samples from the country apply for a permit from the Ministry of Health. However, our informants pointed out that this law is difficult to enforce, and it is possible for samples to continue to leave the country undocumented and unaccounted for at a national level. As suggested by one key informant, “if the information to drive that new diagnostic test fundamentally is derived from clinical samples that arose in South Africa, then we, as a nation, have to do something about controlling that value. And controlling where that value is generated and who owns it. Who owns the information and any spin-offs that come from that downstream.” Consequently, we learnt of discussions in South Africa on how to best capture this value. For example, should South Africans consider extending the current Biodiversity Act to include human samples, or should they take a different approach? It is important, however, that the vital role of international collaborations for South African research is not unduly restricted to the detriment of South Africa. Thus, many key informants view this as a delicate balancing act in which they appreciated that research is a global enterprise and that knowledge should remain public but also emphasizing the importance to South Africa of generating equitable international collaborations that can provide much needed financing and potentially contribute to local scientific capacity building.

5.5 Institutional Leadership

The Public Understanding of Biotechnology programme, initiated by the Department of Science and Technology in South Africa, is mandated to educate the public and stimulate debate on the broad issues of biotechnology. Nevertheless, it is the AGEI that has taken the lead on communicating issues of genomic sciences to the general public. The AGEI is devoted to
educating and engaging with the public about the structure and function of the genome, and about the genetic basis of diseases relevant to the South African population. The AGEI has developed a number of programmes towards this effort. For instance the Living History Project provides the public with the opportunity to discover their genetic ancestry. And the Skin Colour Education Project provides schools and museums with education materials, including published literature and interactive media, on human genomic variation and skin pigmentation. These types of projects are designed, in part, to address the public concerns associated with decades of apartheid rule, thereby establishing trust between the public and researchers. The AGEI also hosts regular seminars, such as the public Darwin Seminar Series, which given the general public the opportunity to engage with leaders in the field.

In addition, and in recognition of the limitations of these types of initiatives, as part of the proposed national EEELSI unit, the Division of Human Genetics is developing a pilot proposal entitled ‘Heritage’. By proposing that human genomic research relates and incorporates the contextual realities of how individuals and communities understand themselves, Heritage aims to transform human genomic research from parachute research to an interactive ongoing process that involves both the humanities and the sciences. For example, through an interactive online system, Heritage could link genetic researchers, anthropologists, linguists, historians, clinicians, government policy makers, the community and the public, with each group contributing and commenting on the description of population groups. If successful, Heritage could transform the traditional research process and result in innovative models, unique to South Africa, for raising public awareness and for obtaining public support. For instance, it could serve as a mechanism for the government to develop contextual public health policy that incorporates genomic, environmental, cultural and health data.
5.6 Local Health Benefits

South Africa is faced with formidable health challenges, notably its current HIV crisis – HIV is its leading cause of death in both men and women (see the MRC’s Burden of Disease Research Unit FAQs at: [http://www.mrc.ac.za/bod/faqdeath.htm](http://www.mrc.ac.za/bod/faqdeath.htm)). It has one of the world’s lowest life expectancies, 50 for men and 53 for women (see the World Health Organization’s South Africa Overview, 2008 at: [http://www.who.int/countries/zaf/en/](http://www.who.int/countries/zaf/en/)), and its long-term economic stability is threatened by its current health crisis. Accordingly, it is not surprising that public investments directed towards innovation in the health sciences must align with South Africa’s health priorities, such as the development of an HIV vaccine. We came across a few relevant HIV-related human genomic variation projects that have been recently implemented or that are in the pipeline. For instance, a study at Stellenbosch University is investigating the genetic basis of the observed differences in response to anti-retroviral therapies in HIV-positive patients of various South African ethnicities.

Another major project is a public-private admixture mapping study recently initiated between researchers at the Centre of Excellence for Biomedical TB Research and GlaxoSmithKline (with additional funding from the Wellcome Trust and the University of Oxford). The study involves up to 1,000 samples from the South African Coloured population. Previous genome-wide scans and genetic variation studies in this population have contributed to increasing understanding of genetic susceptibility to TB, including revealing the novel target loci $MC3R$ (melanocortin 3 receptor) and $CTSZ$ (cathepsin Z). It is hoped that the data generated by the admixture study will make similar contributions. Confirming the limited local capacity faced by South African researchers when conducting scaled-up human genomic variation studies, the
admixture-mapping study samples were exported and the data generation and preliminary analysis was conducted at the Affymetrix laboratories in the United States.

Other smaller-scale studies explore variation within single candidate genes and/or involve Pharmacogenetics studies in several chronic conditions, including cardiovascular disease, obesity, hypertension and fetal alcohol syndrome. For instance, the Institute for Cellular and Molecular Biology recently established at the University of Pretoria and funded by the University, the NRF, the National Health Laboratory Trust and a private pathology group in South Africa is exploring Pharmacogenetics and obesity in sub-Saharan populations. It is clear that the results of these and other future studies would be easier to interpret and utilize if there existed a single national database providing details of baseline variation within South Africa. Not surprisingly, a few key informants suggested that they were in fact investigating the possibility of independently developing databases (either national or regional), with some interviewees intimating that they might introduce fees for commercial use.

Our key informants generally agreed that the lack of local collaboration between university-based academics limited R&D in the field of human genomic variation. We did learn of recent initiatives through the Department of Science and Technology and the MRC to generate multidisciplinary collaborations between local researchers and institutions in an effort to address this challenge. An examples of a successful collaboration is provided by the recent collaboration between the Division of Human Genetics at UCT and the Human Genomics Diversity and Disease Research Unit of Witwatersrand, which was set up to explore genetic variation within indigenous Southern African populations. With shared resources and Affymetrix’s donation of GeneChip Human Mapping 6.0 Array Set, and despite the lack of funding, the researchers were able to complete their study, which they are currently preparing for publication.
In addition, some researchers are attempting to develop a National Functional Genomics Network, with one of the mandates to generate shared access between existing South African genetic databases.

5.7 Knowledge-based Economy

In Mexico, India and Thailand, we found that investment in genomic medicine platforms is in part driven by the desire of these nations to participate in a global knowledge-based economy\(^\text{17}\). The National Biotechnology Strategy for South Africa also highlights the importance of developing a national system of innovation in the biotechnology sector, which includes genomics, in order to enhance global competitiveness and local economic growth. Genomic medicine, specifically pharmacogenomics, is highlighted in this document as a potential industrial opportunity\(^\text{373}\). More recently, the Department of Science and Technology in South Africa produced a report entitled ‘Innovation towards a knowledge-based economy: ten year plan for South Africa (2008-2018)’\(^\text{381}\). In this report, the government highlights genomics and suggests that South Africa should position itself as a major producer in the pharmaceutical and nutraceutical industries through the development of appropriate technology platforms that would be based on local strengths.

So far, South Africa has no national genomic medicine platform comparable to Mexico’s National Institute for Genomic Medicine (INMEGEN)\(^\text{362}\) with its focus on commercialization of locally generated knowledge. Nevertheless, there is evidence of entrepreneurial activity around genomic-based health sciences in South Africa, in both the public and private sectors. The CPGR is a not-for-profit service provider based in Cape Town that was created under the National Biotechnology Strategy. Currently it receives public funds from the Cape Biotech Trust (CBT) and Plant Bio, two of the biotechnology regional innovation centres, to create local capacity and
a knowledge base to increase its scientific output, and to support or drive existing or new commercial interests in the genomic and the proteomic sectors. At current capacity, the CPGR is servicing up to 80 clients, both local and international. Its recent successes, together with the requirement to become self-sustainable over the next few years, have led the CPGR to consider adopting a commercial not-for-profit core. Towards this aim, the CPGR is currently exploring R&D opportunities within genomic medicine, including the development of biomarkers and personalized medicine. Members of the CPGR cite tremendous scientific and business opportunities in the biotech sector in South Africa and their ability to provide low-cost services on the international market as a significant advantage for driving commercial ventures.

Another example is Gknowmix, a private wellness service, which was established in collaboration with Kopano Life Sciences and the South African MRC, the Cape Biotech Trust and Acorn Technologies (a regional business incubator). Although it is too early to determine Gknowmix’s success, it does provide an example of how basic academic human genomic research can be translated into a product or service that uses the existing infrastructure designed to generate a biotechnology sector in South Africa. Gknowmix offers two genetic tests for multifactorial conditions: the Cardiovascular Genescreen and the Wellness Genescreen. The interpretation of the results in the context of specific lifestyle and clinical data constitutes Gknowmix’s intellectual property. By opting to provide health-care professionals with the test results along with their analysis, Gknowmix’s approach addresses the challenge of limited knowledge of genomics on the part of health care professionals.

Nevertheless, key informants raised a number of challenges associated with commercialization of genomics-based research. Some suggested that despite the existence of technology transfer units located in the universities, spinning out companies from basic genomics-based research is
not well established in South Africa and across the life sciences, “researchers struggle with it.” We were also told that the Gknowmix model was not well received by the scientific community, with academics questioning the ethics and usefulness of introducing what they considered to be largely unproven, costly services that will only benefit private health-care payers. As in other countries where such services are being introduced, the regulatory system is not in place to either support or regulate the products and services of genomic medicine as they become available. For instance, Gknowmix is registered with the Board of Healthcare Funders and operates according to the Human Tissue Act, although the type of services that can be offered is not regulated. The South African government will need to anticipate these issues as they arise and develop the appropriate legislation and guidelines to address them. For example, interviewees cited the lack of a genetic privacy act as a challenge. Currently, insurance companies are self-regulated in this respect and it is not known how insurance companies plan to manage genetic information.

5.8 Concluding Remarks

Given the constraints and the early stage of development of the field as a whole, we found an impressive amount of research on human genomic variation in South Africa. Because of the predominance of HIV and TB infections as public health threats, there is an appropriate emphasis on using human genetic variation research to improve health care for these scourges, focusing on drug metabolism and disease susceptibility at the individual and population level. At the basic population-profiling level there has been at least one recently completed substantive collaborative project looking at human genetic diversity among indigenous population groups in South Africa. Moreover, a national large-scale genotyping project to profile the South African population is being considered, along the lines of those established in Mexico and India. As compared with other case studies conducted by our group, South Africa provides a unique
perspective of the feasibility of a privately funded population database; this is an important consideration in countries where public funding is limited. However in these cases stakeholders should develop guidelines on how to maximize access to private resources by local academic researchers in order to encourage basic research.

The well developed public engagement programmes that are in place will go a long way towards facilitating the implementation of genomics-based products and services as they become a reality. However, in order to progress, South Africa will need to pay attention to some of the challenges we identified here. For instance, additional government support in terms of available public funding to help establish research platforms. In addition, although international collaborations contribute to capacity building in South Africa, we learned that they can occur at the expense of local collaborations. The recent report, discussed above, by the Department of Science and technology on knowledge-based innovation in South Africa affirms many of the challenges highlighted by our key informants, including the lack of domestic collaboration and the need for funding to close the gap between basic research and commercialization, and also suggests methods for addressing them.

There is recent evidence of research activity in other sub-Saharan countries. A collaborative effort between African researchers has resulted in the creation of a biobank and pharmacogenetics database representing several ethnic groups (Yoruba, Hausa, Ibo, Luo, Kikuyu, Maasai, Shona, San and Venda) located at the African Institute of Biomedical Science and Technology (AiBST) in Harare, Zimbabwe\textsuperscript{382}. However, the ongoing political turmoil in this country could limit the potential impact of this resource.

The South African government, on the other hand, is committed to science and technology innovation, to establishing a knowledge-based economy, and to harnessing life-sciences research
for health and economic development. Although the relevant policies are in place, what remains to be seen is to what extent they will be translated into concrete support for research, development and delivery of products and services in the human genomics field. Identifying the needs, encouraging local collaborations and helping to form R&D networks will go a long way towards establishing South Africa in this field.
Chapter 6
Illustrating genomic sovereignty

6

6.1 Introduction

As highlighted earlier, the case studies described in chapters 4 and 5 are part of a larger project, on large-scale genotyping projects in the developing world: *Human Genomic Variation: Implications for Global Health* (see Appendix 1, for the these publications). Together, these case studies identified several themes related to the investment in- and development- of the Institute for Genomic Medicine in Mexico (INMEGEN)\(^\text{362}\), the Indian Genome Variation database (IGVdb)\(^\text{383}\), the Thailand SNP Discovery Project and the Thai Center for Excellence in Life Sciences Pharmacogenomic Project\(^\text{339}\), the African Genome Education Institute (AGEI)/Division of Human Genetics at UCT\(^\text{338}\), and the HUGO Pan Asian SNP Initiative\(^\text{17,340}\). More broadly, these themes have contributed to a preliminary framework, for other developing countries looking to invest in large-scale genomic research, as per the 2002 recommendation of the World Health Organization\(^\text{20}\). Table 1 (below) provides a summary of each of the themes.

Table 1: Roadmap to Investing in Large-Scale Human Genomic Research in the Developing World\(^\text{17}\)
Of interest is the theme of *genomic sovereignty*, which first arose in the INMEGEN case study, and was elaborated upon during subsequent case studies. In this chapter, I provide a deeper analysis of *genomic sovereignty* based on my own experience, study interviews, discussions with colleagues, the literature and my own reflection on the subject. I focus on how it may contribute to each country’s aim of achieving health equity through investments in genomics as well as its potential limitations. The chapter starts with a description of the problem. It then highlights the definition of sovereignty and how as a concept it has been linked to the field of genomics. Specifically as it relates to the Convention on Biological Diversity (CBD), viral samples and indigenous peoples. The chapter then reflects on the motivations behind relying on genomic sovereignty by countries in the developing world and its implications, based on a cross comparative analysis of the above listed case studies. Lastly, the chapter examines whether genomic sovereignty is justified, and if so how it may be best conceptualized. The objective of

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**Roadmap to Investing in Large-Scale Human Genomic Research in the Developing World**

**Political Will**
- Government leadership, political support and legislation are important in establishing genotyping projects

**Institutional Leadership**
- Communicating with the public about genomic research, and initial strategic collaborations aid in adopting and advancing research

**Knowledge-based Economy**
- A crucial outcome of these investments is the acceleration of capacity to build scientific research and the ability to internalize new technologies through the developing and maintaining valuable human resources

**Local Health Benefits**
- Investing in genotyping projects can provide these countries with the necessary tools to better understand drug response, disease mechanisms and disease susceptibility in their own populations

**Genomic Sovereignty**
- The concept of genomic sovereignty is linked to the wish of these countries to capture the value of their investment in these genotyping initiatives
this chapter is to set out the scope and significance of state sovereignty as a foundation on which to explore current debates on ownership and access of human genetic materials xxviii.

6.2 International and National Guidelines on Genomic Research

Currently, there is a gap regarding legislation on ownership of- and access to- human genetic materials in large-scale human genomic research. There are several existing international guidelines and statements that provide guidance for the development of genomic research frameworks. I have compiled some of the more prevalent of these mentioned in the literature 56,213 89,214 in Table 2 (below).

**TABLE 2. International Guidelines on Genomic Research**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline</th>
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<tbody>
<tr>
<td>World Medical Association</td>
<td>Declaration of Helsinki (2000)</td>
</tr>
<tr>
<td></td>
<td>Declaration of Ethical Considerations regarding Health Databases (2002)</td>
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<tr>
<td>Council of Europe</td>
<td>Recommendation on Human Tissue Banks (1994)</td>
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<td></td>
<td>Convention on Human Rights and Biomedicine (1997)</td>
</tr>
<tr>
<td></td>
<td>Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin (COM, 2006)</td>
</tr>
<tr>
<td>UNESCO</td>
<td>Universal Declaration on the Human Genome and Human Rights (Unesco, 1997)</td>
</tr>
<tr>
<td></td>
<td>International Declaration on Human Genetic Data (Unesco, 2003)</td>
</tr>
<tr>
<td>Human Genome Organization</td>
<td>Statement on DNA Sampling: Control and Access (HUGO, 1998)</td>
</tr>
<tr>
<td></td>
<td>Statement on Benefit Sharing (HUGO, 2000)</td>
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<tr>
<td></td>
<td>Statement on Human Genomic Databases (HUGO, 2002)</td>
</tr>
<tr>
<td>OECD</td>
<td>Recommendation on Human Biobanks and Genetic Research Databases (OECD, 2009)</td>
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</tbody>
</table>

xxviii The term human genetic materials here, is intended to include genetic samples, the electronic sequence data and the genetic database collection. These terminologies are generally vague in nature, and there is no real consensus on what constitutes genetic materials (i.e.: does it include electronic data and information) in the literature.
These organizations represent various stakeholders at the international level, including international scientific networks (HUGO) and industrialized nations (OECD). Knopper and colleagues (2007) and others have pointed out that they are general in nature, lack consistency and consensus, pay little practical attention to how to address capacity issues, both legal and scientific, are not legally enforceable and do not have clear mandates to develop international norms and standards for collaboration in genomic research.

For instance, in my review of the guidelines, I found that they do not always explicitly differentiate between genetic samples and electronic data. The Council of Europe (COM) (2006) recommendations make reference to ‘biological materials of human origin’, but provide no explicit definition suggesting that they may only apply to genetic samples and not necessarily to the electronic data. Yet, the COM recommendations go on to provide a clear definition for a ‘population biobank’, which “is a collection of biological materials that has the following characteristics: i) the collection has a population basis; ii) it is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects; iii) it contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; iv) it receives and supplies materials in an organized manner” [Italics added]. Whereas, the OECD guidelines focus on human biobanks and genetic research databases which include, “human biological materials and/or information generated from the analysis of the same” [italics added]. A clear definition, and consensus over what is meant by ‘human genetic materials’ is essential for future governance of genomic research. Thacker (2005) has written that, “DNA can exist as biological material in a test tube, as a sequence in a computer database, and as economically valuable information in a patent” [Italics added]. I would add that each instance although inevitably interconnected, raises various unique governance issues at each stage. In addition, his statement
implicitly reflects the fact that economic globalization is an inseparable feature of large-scale
genomic research, where international collaboration is often viewed as synonymous. Indeed,
within the last decade, bioinformatics has rapidly evolved as a field and genetic information is
increasingly, sometimes exclusively, stored and transferred beyond national borders as electronic
data. Accordingly, the focus of guidelines and policies is shifting from human biological samples
to the electronic data – and there remain analogous pressures on researchers to share electronic
data, across national borders, that is generated by scientific communities and funding bodies 386-
389 (Also see: http://www.gatesfoundation.org/global-health/Documents/faq.pdf, accessed May
20, 2011]. These policies and guidelines however raise similar concerns, as those featured in
Table 2, as they also lack consensus on ownership and control of data xxix 390.

In addition, the guidelines featured in Table 2 lack universal agreement on the status of human
genomic materials and at times, can appear contradictory. For instance, UNESCO (1997) refers
to the human genome as follows, “[I]n a symbolic sense, it is the heritage of humanity” 191,
whereas HUGO (1995, 2000, 2002) states that, “the human genome is part of the common
heritage of humanity” 201,391,392 [italics added]. HUGO [2002] also recommends that “[H]uman
genomic databases are global public goods” 201. Each of these terms is based on differing
assumptions. The common heritage of mankind is based on justice and international law and is a
form of res communis or common (public) property 192. Whereas, global public goods (GPG) are
based in economic theory and property law and, in their purist form, are considered non-
excludable and non-rival, while their benefits are universal (countries, people and generations)
205. I expect that human genetic materials, if considered a GPG would likely fall between a pure

xxix Personal conversation with Dr. Claudia Emerson, an expert in the field of data sharing, she proposes a series of
principles, which together, can provide a broad framework for data sharing. These include: reciprocity, respect,
promotion of the common good, stewardship, proportionality and accountability [Emerson, unpublished].
GPG (knowledge) and a regional club good (information networks). This would reflect that they are non-rivalrous, but possibly excludable due to existing inequities in access (limited capacity). Moreover, an argument could be made against the idea that the expected benefits are truly universal, although that is beyond the scope of this chapter. GPGs also have additional dilemmas, as I highlighted in Chapter 2, raised by the need to generate access goods and promote and facilitate collaboration (who is responsible and how can this be best facilitated remains unresolved). Similarly, the ‘common heritage of mankind’ also requires that all stakeholders (mainly countries) share in the management and benefit. In the case of human genetic materials however, Boggio (2008) documents that stakeholders consider the designation vague. Bovenberg (2005) has also argued that when applied to commercialization and benefit sharing frameworks, it lacks practicality. Moreover, these statements were generated without wide consultation in the developing world. As one interviewee in my research pointed out, “From the perspective of South Africa, my biggest disappointment was that we did not have dialogue regionally on those points in the declaration, to kind of constructively contribute to a world view.”

The guidelines and recommendations in Table 2 do achieve consensus on one aspect, which is that every effort should be made by those involved to share human genetic materials in an effort to contribute to the common good. It is generally believed by stakeholders that large-scale genomic databases are a critical form of scientific infrastructure that is pre-competitive in nature. Research consortia, such as the Human Genome Project and the International HapMap Consortium have exemplified this view and as consortia, they continue to encourage sharing of human genetic materials and placing data in the public domain. For the most part however, I find that although the international recommendations and guidelines also encourage these principles,
they do not provide a single best practice. Instead the guidelines and recommendations suggest that best practices will differ contextually.

In reality there also remains a lingering hesitancy to share human genetic materials, as well as on-going references to concerns regarding bio-colonialism, bio-piracy and bio-exploitation. These concerns are often specific to developing countries, where there exist significant opportunities for studying human genomic diversity and limited local research capacity. The lack of consensus and limited effect of existing international recommendations and guidelines may explain why. It may also reflect, as per Hsieh (2004) that “although international statements can provide guidance, normative standards are created predominantly through the influence of state practices” 55. It is not surprising then, that a handful of countries, mainly developing nations, have exerted jurisdictional control, through national guidelines or legislation (e.g.: Mexico 362, India 354, China 396,397, Iceland 104,118, Estonia 124) over human genetic materials.

Wolfgang van den Daele (2008) has argued that these reactions are inevitable, given that, “the public domain as a constitutive feature of the knowledge society will come under pressure from two sides: In the West (or North) from the side of companies that lobby for more extensive and longer patent and copyright protection, and in the South from the side of developing nations that nationalize genetic resources” 398. Indeed, this was also reflected in my research as some participants were quick to point out that developed nations simply were not confronted by these choices as the existing capacity and infrastructure negated the need to ship samples elsewhere.

The existence of national legislation and guidelines can be considered as attempts to recognize human genetic materials at the national level as sovereign. For instance, in Mexico, the 2008 amendments to the General Health Law that restrict the export of genetic material from Mexico 362 (Also see: Appendix 5 for a copy of the Legislation both in English and Spanish;
http://www.jornada.unam.mx/2008/03/28/index.php?section=sociedad&article=046n1soc have been referred to by both the Mexican media and INMEGEN staff as ‘genomic sovereignty’.

Knoppers (2007) has argued that national legislation is also limited as they “are only enforceable in national jurisdictions” and they fail to address the necessary “networking” of genomic databases. The 2009 OECD Guidelines on Human biobanks and Genetic Research Databases noted these gaps of legislation and the critical need to address them in the annotations, where they added that, “The transfer of human biological materials and data outside the geographical jurisdiction where they were collected raises numerous complex issues. […] there may still be lacunae and more specific legalization, regulation and policy may be required”. These complex issues include the ethical dilemmas of ownership and access to human genetic materials. An obvious question then, is whether sovereignty over genetic resources is indeed justified. To begin to approach such a question, we must first define sovereignty and consider its agreed upon principles.

6.3 Sovereignty Defined

The concept of sovereignty itself is ambiguous at best, and through time, the principles, which underlie the concept, have shifted and changed to meet the demands of the era (e.g.: authority and territoriality). Scholars have argued that as a concept it is complex, if not impossible to define. Most would agree that modern state sovereignty, as an institution, arose out of the Peace of Westphalia in 1648, and was further codified in the 1933 Montevideo Convention on the Rights and Duties of States requiring a permanent population, a defined territory and a functioning government. Sovereignty as a modern concept can be primarily understood as supreme authority within a territory. The key principles resonate here are that of authority and territoriality.
State sovereignty, which is the focus of this chapter, can be conceptualized as both institutional and legal, where the institutional element focuses on identifying those institutions, which are granted legitimate authority to establish, monitor and enforce legal sovereignty. Authority itself is supreme, mutually recognized and legitimated through a body of law (e.g.: international law, constitution). It is rarely considered absolute and it can be an individual, a committee, the people, or even the constitution. To some it is the exclusive right to determine what is political. As a system, state sovereignty can have the following features, best described by Schrijver (2000), “that the government of a State exercises public authority, enacts legislation, asserts a monopoly over the legal use of force, levies taxes, issues currency, maintains law and order, exercises justice, offers protection to citizens, fosters the observance of the rights of individuals, peoples and minorities and sets out the main lines of public policy”.

And as summed up by Kelsen (1960), “‘sovereignty’ of the state means only that the state is not subject to a legal order superior to its own legal order, i.e., the national law”.

Territoriality, the basis of international relations, refers to geographic boundaries and can be linked to the notions of ownership and property. Indeed, some have argued that sovereignty can only be understood in terms of property rights, which allocate material resources through the mechanism of rules. Sovereignty also has both internal and external features, those principles listed above are features of both, whereas additional principles commonly associated with the external aspect of sovereignty are mutual recognition (reciprocity) and non-intervention between states, which reflect an assumed equality between sovereign states, and increasing inter-dependency. Sorenson (1999) describes non-intervention as “the prohibition against foreign interference in the domestic affairs of other states” and reciprocity as the “exchange of roughly equivalent values”.

Lowenheim and Paltiel (2004), on the other hand, argue that the “mutually constitutive element of self-restraint/mutual recognition” of
sovereignty pre-supposes a hierarchy of among states (led by the ‘great powers’), which is respected through justice, not equality and non-intervention. At present, there are a number of internationally recognized limitations to state sovereignty that originated within the Charter of Rights by the United Nations (Charter). These include Article 1 (2) which stipulates that “(a)ll Members, in order to ensure to all of them the rights and benefits resulting from membership, shall fulfill in good faith the obligations assumed by them in accordance with the present charter.” The Charter further compels states “to achieve international cooperation in solving international problems of an economic, social, cultural, or humanitarian character and in promoting and encouraging respect for human rights and for fundamental freedoms for all, without distinction as to race, sex, language, or religion.” There are also a number of pressures, which have arisen in recent decades, on state sovereignty, including: self-determination movements and globalization. Self-determination movements result in a schism between national sovereignty (defined population) versus state sovereignty (state authority). Barkin (1994) writes that the results are often largely dependent upon what international norms legitimize; a common example includes indigenous self-government, in which it is rarely possible to satisfy the demands of the established state and the nationalist claims of indigenous peoples. Globalization, on the other hand has given rise to increasing inter-dependency between states and credence to non-state actors (e.g.: epistemic communities, multinationals and NGOs). As these dilemmas arise and place increasing pressure on state sovereignty, scholars argue that the concept itself may no longer be relevant as a tool to frame national governance and international relations. For instance, some argue that external sovereignty is currently compromised by globalization; States now must capitulate to external pressure to cooperate, thus compromising their territorial integrity. Schrijver (2000) on the other hand
disagrees with this conclusion and from an international law perspective examines the concept through a ‘sovereignty test’ [Table 2, see below], a series of questions, which he suggests can provide a “greater understanding of and some insights into the qualifications of sovereignty”\textsuperscript{404}.


<table>
<thead>
<tr>
<th>Sovereignty Test</th>
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<tr>
<td><strong>1. The actors.</strong> Are states preserving the prerogative of international action for themselves? Furthermore who are the creators of law? Who are the participants in legal discourse?</td>
</tr>
<tr>
<td><strong>2. The definition of sovereignty.</strong> How is sovereignty conceived? What qualifications have been added?</td>
</tr>
<tr>
<td><strong>3. The scope of sovereignty.</strong> Is this territorially defined? Is extra-territorial jurisdiction also being sought? Is there a question of shared sovereignty?</td>
</tr>
<tr>
<td><strong>4. The influence of universal values.</strong> What justifications are employed for subjecting sovereignty to international law and hence qualifying it, and what is the influence in this regard of certain universal values?</td>
</tr>
<tr>
<td><strong>5. Duties of states.</strong> Which duties incumbent on states emanate from rules of substantive law which limit the discretion of states to formulate their own policies unilaterally? What are their duties on the international stage?</td>
</tr>
<tr>
<td><strong>6. The role of international institutions.</strong> Is there a transfer of some aspects of state sovereignty to supranational entities and what form do those entities take?</td>
</tr>
<tr>
<td><strong>7. Procedures for settlement of disputes.</strong> Are effective procedures for international settlement of disputes being introduced, so that he implementation of obligations is no longer solely a sovereign function?</td>
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In emphasizing “the influence of universal norms and values, the role of international organizations and the appropriateness of international procedures for the settlement of disputes”\textsuperscript{404}, Schrijver (2000) writes that in an age of increasing globalization and international law, the state remains the “main instrument for implementing such newly-established rules and the main body to be held internationally accountable for their observance”\textsuperscript{404}. He agrees that “the circle of participants in the legal process is expanding beyond States and State-based organizations, the
influence of universal values on the process of development of law affecting State sovereignty is becoming greater, the duties of States are increasing and the role of international organizations in implementation and monitoring is steadily expanding". However he also demonstrates, through the use of his ‘sovereignty test’ that the state itself, as the implementer and one of the only recognized units in international law, remains critical, thus revealing the necessity of the state in establishing and maintaining international cooperation towards shared goals. In doing so, he concludes that sovereignty, at the international level, can be considered an, “organizational principle” and the “source of responsibility, accountability and liability and as the basis of international cooperation”.

6.4 The Evolution of Genomic Sovereignty

As I have mentioned above, a handful of countries have exerted jurisdiction over human genetic materials, mainly genetic samples, through national legislation. There are, however, several informative examples in the literature of how the concept of sovereignty has been more explicitly applied in debates over ownership of- and access to- genetic materials. These are the Convention on Biological Diversity (CBD), Indigenous peoples, and Indonesia and the influenza virus.

6.4.1 The Convention on Biological Diversity

In 1983, pre-dating the announcement on the Human Genome by UNESCO, the Food and Agricultural Organization (FAO), an arm of the UN, adopted a resolution declaring plant genetic resources as the ‘common heritage of mankind’, and as such available “without restriction”. Common heritage of mankind has also been applied to “the deep seabed, outer space, and the Antarctic”. And, for the most part, in these instances, developing nations had
been supportive, if not the initiators. Especially as these were considered international territories, which may yield valuable resources and developing nations wanted some guarantee that the potential benefits would not be exclusive to those nations who had the economic and technological means to exploit the resources. Nevertheless, in the case of ‘plant genetic resources’, the stance ignited a slightly different debate between developed and developing countries. Developing world politicians and activists accused the developed world of exploiting the wealth of genetic materials located in the developing world. They raised concerns that plant genetic materials were taken from developing countries as a raw material at no cost (as the common heritage of mankind). The relevant information was then extracted, and if valuable, patented, and incorporated into a product with an assigned value, and oftentimes, limited affordability. Moreover, they accused groups, such as the Consultative Group on International Agricultural Research (CGIAR), of extracting plant genetic resources under the guise of foreign aid. Some even went so far as to accuse scientists and pharmaceutical companies located in the developed world of ‘bio-piracy’, considered the “the unauthorized and uncompensated removal of genetic resources from a source country, which is usually a developing country”.

As an alternative, Kloppenburg and Kleinam (1988) proposed early on that plant genetic resources be considered “national property” instead of “common heritage” as an equitable solution to the impasse between the developing and developed countries. These debates were the foundation of the negotiations that saw the Convention on Biological Diversity (CBD) frame non-human genetic materials, along with the traditional knowledge that is oftentimes associated with them, as sovereign resources. These debates were also considered by some as the inception of claims that saw the politicization of genetic resources (bio-politics).
The CBD itself, entered into force in December 1992, and as of today, has 168 signatories. The main objectives of the CBD are: the conservation of biological diversity; the sustainable use of the components of biological diversity; and, the fair and equitable sharing of the benefits arising out of the utilization of genetic resources. Under Article 15 of the document, the CBD recognizes state sovereignty over biodiversity resources and that “authority to determine access to genetic resources rests with the national government and is subject to national legislation.” However, in an effort to also ensure equitable access and benefit sharing occurs, the CBD also stipulates under Articles 15 and 19, that countries will facilitate access in a fair and equitable manner and facilitate sharing of any benefit arising from said genetic resources. Equally important, during the initial negotiations, there were also calls by some to extend sovereignty to human genetic materials, however these attempts were unsuccessful as many participants felt that they did not fall under the CBD’s mandate and would raise serious ethical dilemmas. The Bonn Guidelines, issued in 2002, set out a series of instructions to “assist ‘Parties’, Governments and other stakeholders in developing overall access and benefit-sharing strategies, and in identifying the steps involved in the process of obtaining access to genetic resources and benefit-sharing.” Notably, Oldham (2004) points out that the emphasis placed on mechanisms, such as the Material Transfer Agreement (MTA), demonstrated that negotiators were specifically focusing on genetic samples, and that they had yet to address the “increasing

xxx That this happened came up in several discussions with key informants in India and South Africa.

xxxii A Material Transfer Agreement is “a contract that may be used to govern the transfer of research materials – samples and data – between biobanks and researchers. MTAs set forth the terms for giving researchers access to biological specimens and associated information. They typically define the rights and responsibilities between both parties with respect to the materials and any derivatives.”
trend towards electronic transfers because genetic material can be readily expressed as

*information*”.

The CBD represents the first, and thus far only, *international* and legally binding recognition of state sovereignty, as an approach to manage genetic materials. In that sense, it recognizes the principles of mutuality and non-interference embodied in sovereignty that I outlined in the previous section. Yet, since its implementation, it has been subject to several criticisms, which reflect the inherent limitations of sovereignty generally. First, although the document is legally binding, it is only so for those states that are signatories; importantly the U.S. has yet to sign. Brody (2010) has argued that the U.S. is not opposed to sovereignty over biological resources within a state’s recognized territory, per se. Instead, he has implied that it is the subsequent assumption, held by the CBD, that a state could assert sovereignty over the use of the “genetic information to develop new products that can be patented” 431. Given that the U.S. has granted 58,256 DNA patents as of April 29, 2011 432, it is more than obvious as to why the U.S. would object to the CBD concept of sovereignty. The objection highlights the ongoing difficulty of stakeholders to differentiate between the spectra of genetic samples, the electronic data, and the information derived from the data, and the critical need to do so. Second, although the CBD recognizes state sovereignty over non-human genetic materials, it is tempered by the accompanying condition of access and benefit sharing, included as a nod to distributive justice and a solution to bio-piracy and the shared mandate of the CBD. These conditions provide similar stipulations as would be expected had non-human genetic resources been recognized as the ‘common heritage of mankind’, raising the question as to whether recognizing genetic materials as sovereign is merely a game of shells, with the focus really being on benefit-sharing as a tool to ensure distributive justice.
Lastly, indigenous peoples maintained early on that the CBD acknowledged them as mere ‘stakeholders’ as opposed to self-determined peoples. They accused the ‘Parties’ of the CBD of placing too much priority on “legitimizing the commodification and commercial exploitation of traditional knowledge of genetic resources rather than protecting this knowledge as a foundation for pursuing the sustainable use and conservation of biodiversity” 430. These criticisms stress the complexity in determining ‘legitimate authority’ in light of ‘self-determination’ movements within states – notably, in the case of indigenous nations, whose rights are recognized in the United Nations General Assembly Resolution 61/295 within the Declaration of Indigenous Peoples 433.

6.4.2 Indigenous Peoples and Genomic Sovereignty

The Human Genome Diversity Project (HGDP) was initiated in 1991, several years prior to the 1997 announcement by UNESCO that the human genome is the “heritage of humanity”. The HGDP organizers, held similar objectives to the CBD and intended to record human diversity by tissue sampling up to 500 global populations, which could then be preserved and stored as part of an effort to document the global genetic variation of the human species. Those involved stressed that, as isolated tribal groups were increasingly disappearing it was imperative that there was a coordinated attempt to record the diversity of these populations before they were forever lost 59,62. A statement that Debra Harry (2010) rightly viewed as disingenuous, “to be clear, saving genes does not constitute saving cultures or people” 434. The HGDP met with early opposition from many of the world’s indigenous groups, some who went so far as to accuse the HGDP of being a ‘vampire project’ 204. Indigenous groups, released resolutions recommending that indigenous people “reject and condemn the Human Genome Diversity Project”, including the World Council of Indigenous Peoples, ‘Resolution of the Human Genome Diversity Project’
of 1993 and the ‘The Declaration of Indigenous Peoples of the Western Hemisphere Regarding the Human Genome Diversity Project’ of 1995. These approaches all reflected the beliefs held within indigenous groups and, at the time, that researchers intended to exploit their genes, sacred life forms and foods for commercial gain; researchers are ‘helicopter scientists’, who drop into communities citing important research and then quickly leave without following up with the community; and, human genomics, more broadly, challenges the spiritual basis of their existence. Indeed, several studies in indigenous groups, specifically targeting common complex diseases, demonstrate why these concerns arose.

First is, the Arthritis Biomarker Study with the Nuu-chah-nulth [Nootka], members of the First Nations in Canada on North Vancouver Island. Researchers were aware of the high incidence of arthritis within the population; considered at the time to be one of the highest rates in the world. In the 1980s Prof. Richard Ward, then conducting research at the University of British Columbia, collected samples of blood from 833 members to study for arthritis biomarkers related to rheumatoid arthritis. He never actually found the gene of interest nevertheless he later shared the collected tissue samples with various researchers. These samples were subsequently used in a number of separate studies including a genetic anthropology study identifying Nuu-chah-nulth as a distinct indigenous population going back over 70,000 years that both challenged their respective creation myth and raised significant economic concerns regarding land claim negotiations. Another potentially harmful project was on the spread of lympho-tropic viruses by intravenous drug abuse. In 2004, following Dr. Ward’s death, the samples were returned to the Nuu-chah-nulth, who now review over research requests for any future studies. Second was research in the southwestern U.S. on the Havasupai tribe. This tribe is known amongst researchers as having one of the highest incidences of type-2 diabetes in the world. For this reason, Arizona State University researchers were
interested in conducting population-based genetic research within the community. On the one hand, the Havasupai accused researchers at Arizona State University of using the samples for studies other than those they gained consent for. On the other, researchers at ASU claimed to have done nothing of the kind, and were convinced there had been a misunderstanding. In response, the Havasupai sued the ASU for $75 million in damages. A separate university investigation yielded two dozen published articles based on the genetic data obtained from the Havasupai blood samples, with one on schizophrenia demonstrating “a high degree of inbreeding” as well as another anthropological study identifying the groups origins (Bering Straight Theory); again demonstrating potential social and economic harm to the community. In April 2010, it was reported that a settlement had been reached and the university would “pay $700,000 to 41 of the tribe’s members, return the blood samples and provide other forms of assistance to the impoverished Havasupai.” The settlement specifically highlights the conflicting nature of informed consent, where, as already mentioned in the literature review, there is an increasing trend towards obtaining broad-based consent from donors to genomic databases. The decision should give pause to those who would consider broad consent as an ideal model for informed consent, as it has demonstrated the need to account for the diverse societal and national interests that arise in human genomic research. The settlement with the Havasupai also differs from previous legal cases in the United States (e.g.: Greenburg and Moore) where downstream control to genetic samples had been denied. However, the focus of the courts in the case of the Havasupai was on the scope of informed consent, not ownership of- and access to- genetic material and certainly not sovereignty.

There have been several well documented cases of controversial attempts to patent genes isolated in indigenous peoples, including the Guyami of Panama, the Hagahai of Papua New Guinea, the Melanese of the Soloman Islands and most recently, the Maasai of West and South
Africa. Oftentimes, these have been misrepresentations of the fact, but they nevertheless raise important misunderstandings between the communities, the researchers and the general public in those countries. For example, in 2009, South African researchers complained that the University of Maryland in the U.S. had patented a Maasai gene mutation, which allows for higher milk tolerance, collected from Kenya, Tanzania, Sudan and South Africa. The accused researchers claimed that the application was not made for any commercial gains but to protect the invention from bio-prospectors. The actual patent itself is a process, developed by the accused researchers employing the sequence data that could be applied to industrial purposes. One of the local researchers involved in the data collection (but not the patent application), Dr. Omar was quoted as saying, “If not patented any commercial group can exploit it and no gains would go to the local communities”. Although there is evidence of a misunderstanding, I would argue that in this case, these occurrences should not be dismissed out of hand. They highlight the increasing need for discourse between the various stakeholders. In addition as I have already outlined, they demonstrate the perceived interconnection between genetic samples, the electronic data, the information and the intellectual property.

Harry (2010) has pointed out the failure of existing national and international guidelines on genetic databases in this respect, as there exist few means for indigenous peoples to hold researchers accountable to their communities once their genetic samples leave their respective territories. Thus as rightly highlighted by Jacobs and colleagues (2010), “the struggle of indigenous peoples worldwide to achieve recognition of their sovereignty and rights of self-determination informs the discussion about biomedical research”. These and other early controversies led to the formation of organizations such as the Indigenous Peoples Council on Biocolonialism (http://www.ipcb.org/), with the stated mission to “assist indigenous peoples in the protection of their genetic resources…” who document and publicize instances of ‘bio-
piracy’ within indigenous communities across the globe and provide policy documents promoting ‘tribal sovereignty over genetic resources’, similar to that in the CBD but nation-based versus state-based, in this case. And this has been applied in some cases, for instance in the United States tribal groups have sovereignty over their jurisdictions and consequently regulate human-subject research conducted on reservations through institutional review boards, such as the Navajo National Human Research Review Board \(^434,444\). Additionally, in Canada, the research guidelines issued by the Canadian Institute for Health Research \(^445\) recognize the sovereignty and right of self-determination as described in the United Nations General Assembly Resolution 61/295 within the Declaration of Indigenous Peoples \(^433\) of the Inuit, Indian and Métis peoples \(^444\). These instances however, are limited and do not govern those indigenous peoples in the United States or Canada who do not live in the representative jurisdictions. Also, as mentioned above, it does not necessarily govern the material that has subsequently left the jurisdiction. These limitations are best demonstrated by the Havasupai case, which saw the return of their human genetic materials on the basis of a breech of informed consent and not sovereignty over the materials. Of course the conflicting nature of ensuring that indigenous peoples benefit from on-going genomic research as well as that they are not exploited through bio-colonialism and bio-piracy are what lie at the center for this debate. Jacobs and colleagues (2010) however, have demonstrated that this is evolving as increasingly national guidelines on genomic research with indigenous populations incorporate individual and community approval on secondary uses of data and samples through community engagement as well as benefit sharing and collaboration with the communities \(^444\).
6.4.3 Indonesia and Viral Sovereignty

In December 2006, the Minister of Health in Indonesia, Dr. Siti Fadilah Supari, made headlines when she saw fit to stop sharing patient samples affected with H5N1 with the WHO, as per the duties established by the International Health Regulations (IHR), the World Health Assembly (WHA), and the Public Health Emergency of International Concern (PHEIC) 446. She based the decision on her claim that Indonesians had not received the appropriate assurances from the WHO that the resulting diagnostics and therapeutics would be affordable to the Indonesian population 447-450. Moreover, patents were being issued to scientists in the developed world on genetic sequences of the ‘Indonesian viruses’ 449. In addition, Dr. Supari ceased to provide ‘timely notification’ of outbreaks to the WHO’s Global Influenza Surveillance Network (GISN) and threatened to shut down the U.S. Naval Medical Research Unit Two (NAMRU-2), a disease surveillance facility 446,447. Notably, she coined the term ‘viral sovereignty’, to which she argued for “a nation’s right to control all information on locally discovered viruses…” 447. Many of Dr. Supari’s concerns were compelling, indeed, from 2005 to 2007, Indonesia had the highest reported number of human H5N1 cases, and it was well-recognized that global capacity for vaccine production and distribution was limited with priority given to several nations located in the developed world 446,448. Regardless, critics accused the Indonesian government of “moral blackmail” 448 and promoting “self-destructive, anti-Western sentiments” 447; they argued that while the CBD and the FAO provided for similar sovereign approaches, in the case of viruses, which did not respect borders and could lead to global pandemics, the approach was “dangerous folly” 447 and a “threat to global health security” 449. While, it is clear that, in some respects, the Indonesian government was promoting an inexcusable state of paranoia by accusing NAMRU-2 and international drug companies of using samples to develop bio-warfare 447,450,451, the
Indonesian government also managed to leverage the human H5N1 samples towards establishing a framework for sharing virus samples, Resolution WHA 60.28, ‘Pandemic Influenza Preparedness: sharing of influenza virus and access to vaccines and other benefits.’ that guaranteed its citizens equitable access and distribution of avian influenza vaccines and therapeutics\(^{449-451}\). The latter move was endorsed in a statement made by the following civil society organizations: the People’s Health Movement, Third World Network, Medico International, Gonoshasthayea Kendra (Bangladesh), AHED (Egypt), Health Unlimited, Asian Community Action Network, All India Drug Action Network, Initiative for Health, Equity and Society (India), Consumers’ Association of Penang (Malaysia), Institute of Science and Society (U.K.), Palestinian Medical Relief Society, PHM Latin America, PHM United States, PHM South Africa, and PHM Australia and New Zealand\(^{451}\). Most importantly, the Indonesia case demonstrates the intrinsic value accorded to human genetic materials.

For each of the above-instances that I have examined, the CBD, indigenous peoples and viral sovereignty -- there is a clear demonstration of the use of the concept of sovereignty to frame debates over ownership and access to genetic material. For the most part, I have found that in these cases sovereignty is leveraged in an attempt to prevent bio-piracy and address the inequity of access, which can and does arise in genomic research. However, I have also found that there are slight differences in each instance as to how the concept has been applied. First, on the one hand, within the CBD, ‘genetic resources’, which are loosely defined in the Convention, under Article 2 as “genetic material of actual or potential value”\(^{426}\), are considered to be sovereign resources, at the level of the state. The same has been argued for the genetic material in the ‘viral sovereignty’ case, although the actual biological materials themselves were obtained from patients. Nevertheless, the debate occurred at the level of the state. On the other hand genetic material has also, in special instances, fallen under the purview of indigenous
sovereignty and self-determination thereby limiting state jurisdiction. Second, as Benjamin (2009) has previously stated, indigenous peoples have employed sovereignty as a tool, largely to “opt out” of genomic research. The Indonesian government, on the other hand leveraged sovereignty to ‘level the playing field’ and guarantee access to the subsequent benefits of genomic research. These approaches are both in contrast to the CBD, which recognizes sovereignty to facilitate access to genetic resources. In summary then, the CBD and the Indonesian government relied on the concept of sovereignty as a mechanism to redress a current imbalance inherent in the current international system, equitable access to the benefits of genomic research. On the other hand, Indigenous peoples, in petitioning the CBD and in human genetic research, employ sovereignty as a tool to prevent bio-exploitation and ensure ethical and appropriate use of genetic materials as per their belief systems. These differences, though slight, are important as they highlight the intricacies of the motivations behind genomic sovereignty.

Each of these examples also reflects the inherent limitations of sovereignty. Thus the answer to the question highlighted earlier, whether sovereignty over genetic resources is justified, remains unclear. Indeed, Brody (2010) and others have argued that alternative theories of justice as represented in the ‘common heritage of mankind’ or the ‘global commons’ concepts are better suited. Indeed, I would agree that this might be the case if the main objective is to ensure equitable access to the benefits of genomic research.

A cross-comparative analysis however, of all of the case studies described in Chapter 3 provides additional key insights into the above-stated question. In “Genomic medicine and developing countries, creating a room of their own”, we generated a preliminary framework, based on empirical evidence, for developing countries wishing to develop locally led large scale human genomics programs. We proposed that, in the early stages, along with institutional
leadership, political will, the focus on local health benefits and the desire to enter a knowledge-based economy, genomic sovereignty is a key feature.

6.5 Genomic Sovereignty: A Working Definition

In Mexico, an amendment initiated by INMEGEN was made to Mexico’s General Health Law that aims to protect the national sovereignty of Mexicans over genetic material. It does so by making it illegal to transport samples of human genetic material outside of Mexico without prior approval from the National Ministry of Health (SSA) \(^{17,362}\). In addition, India has long established guidelines for the Exchange of Human Biological Material for Biomedical Research Purposes \(^{354}\). In Thailand, there are institutional regulations regarding the export of genetic materials, however there are no unified guidelines or regulations \(^{339}\). Finally, in South Africa, there are established regulations in the Human Tissues Act regarding the export of human tissue, but they have yet to be explicitly extended to include genetic materials \(^{214}\), despite ongoing negotiations and a draft amendment initiated in 2007 \(^{214}\). Currently, there is however, a push by South African researchers to adapt the legislation to address these gaps and with the new proposal for a Southern African Human Genome Programme \(^{214,453}\), where stakeholders have expressed a desire to establish genomic sovereignty \(^{xxxiii}\).

Drawing from the cross comparison of these case studies, I will demonstrate that the theme of genomic sovereignty consists of three main sub-themes, an economic argument; a key to public support, and; patrimony. These sub-themes are interlinked, with only slight differences, but as I have indicated above, the differences are important to the question of whether sovereignty, as a mechanism to resolve debates over genetic materials, is justified.

\(^{xxxiii}\) Personal communication.
6.5.1 Genomic Sovereignty: An Economic Argument

An analysis of the data indicates that the concept of genomic sovereignty is in part based on an economic argument. The act of claiming sovereignty over genetic resources can provide developing countries with the opportunity to legislate human genetic materials as an economic resource. In this sense, it is linked to the wish of these countries to capture the value of their investment in these genotyping initiatives. These investments represent locally led, nascent capacity building in the field of human genomic sciences, with an overall long-term aim to eventually be able to generate local health solutions and compete in the global knowledge-based economy. As a result, it is crucial that these projects are given the opportunity to develop in a protected setting.

Several quotes from interviewees in my studies capture this understanding:

“First world countries have the best resources (...) so it is very hard for us finding an area of opportunity, awfully difficult if we talk about technology and electronics and computing (...) if you talk about genetics and genomics being so particular in our population, having this huge resource, that is our history and I definitely think we can do it.”

“If oil of Alaska can be shared by everybody, Indian genome of India can be shared by everybody. But the fact is oil of Alaska is not shared by everybody.”

“...if the information to drive that new diagnostic test fundamentally is derived from clinical samples that arose in South Africa, then we, as a nation, have to do something about controlling that value. And controlling where that value is generated and who
own it. Who owns the information and any spin offs that can come from that
downstream.”

These quotes also highlight the implications highlighted by this argument. First, interviewees
often referred to human genetic material as a resource. In these projects, which are considered
economic investments towards competing in a global bio-economy, human genetic material
forms the raw resource necessary to establishing local scientific infrastructure and capacity. In
the second quote, for instance, the informant draws an analogy between the Indian genome and
oil and mineral resources, which are traditionally exploited to generate national wealth, are
considered sovereign resources and have controversial histories with respect to colonialism and
economic development. Although natural resources and human genetic material are not
completely analogous, clearly there are similarities. Second, as with earlier examples, there is
little to no differentiation between sample, information and knowledge, when referring to human
genetic material as a resource. This may represent the recent and rapid growth of bioinformatics
and a lack of clarity on its impact on re-defining the substance of genetic material. However, as
with the CBD and the U.S., the lack of clarity on this issue will create a serious challenge when
attempting to establish governance and attribute value. As I have already reviewed, for the most
part, there is a global consensus that human DNA samples are not property, as the ramifications
are seen as too controversial. This stance is reflected in most existing legislation which does not
allow for ‘ownership’ and provides opportunities for withdrawal and return of samples to the
original donors. It is however, less clear with respect to the electronic data and information,
especially as it is amassed on a large-scale within a database. There is an international trend
towards considering these materials as ‘common heritage’ and ‘global public goods’ and genomic databases as ‘global public goods’. In large part, this trend is
intended to facilitate international sharing and collaboration that is necessary in large-scale
genomics research. However, these trends may be in conflict with the expressed desire by these countries to leverage these investments towards competing in a knowledge-based economy\textsuperscript{17}. Especially if the data and information amassed in genetic databases are considered to be an economic resource. Foray (2004) defines a knowledge-based economy as “essentially economies in which the proportion of knowledge-intensive jobs is high, the economic weight of information sectors is a determining factor and the share of intangible capital is greater than that of tangible capital in the overall stock of real capital. These developments are reflected in an ever-increasing proliferation of jobs in the production, processing and transfer of knowledge and information”\textsuperscript{454}. Thus, I would argue, that where knowledge and information were once viewed as universal and unbounded, it can be argued that in a knowledge-based economy they are partially subsumed as competitive resources. Indeed as per Mitchell and colleagues (2010), “the bio-economy, or at least its biomedical aspect, is based on human tissue fragments, which can be analyzed, reformulated, and altered in vitro to make them bio-valuable, to yield surpluses of both profit and health, often through the transformation of tissues and information into commodities”\textsuperscript{455}. Here is where I propose state sovereignty then becomes relevant and possibly more effective than ‘common heritage’ and ‘global public goods’ tools. Historically technology and production were the basis for state sovereignty\textsuperscript{209}, in a knowledge-based economy on the other hand, information and knowledge may also form the basis, thereby creating an economic argument for state sovereignty over human genetic resources.

6.5.2 Genomic Sovereignty: A Key to Public Support

An analysis of the data indicates that the concept of genomic sovereignty is also linked to promoting a nation’s genetic heritage, and the wish of these countries to generate public support for these initiatives. Genetic heritage is the belief that genetic material is a form of cultural
property. Genetic heritage featured in both the case studies in Mexico, South Africa as well as the HUGO Pan Asian case study. Participants saw it as a method to generate enthusiasm in the general public to participate in large-scale genotyping initiatives, often as nation building projects, as captured by the following statements from my interviews:

“Now, in actual fact, where potentially this kind of information is more beneficial is in national pride. I’m unique that as a Mayan Indian, say, I’m unique. And in a world where people have been oppressed for a long time, that says a lot.”

“...there is a big buy in towards genetic heritage as part of our heritage day celebrations [...] people would come and ask me to give talks, and you know, to engage in radio and newspapers article on, talking about the genetic heritage of the peoples.”

“Let’s ask the question, how much are we alike? How much are we different, you know? More, how much are we alike? And use it as sort of a social political statement of Asianess...”

These statements reflect arguments by Upshur and colleagues (2006) who wrote that “[T]he analysis of tissues in the same geographical and cultural milieu from which they have been taken may enhance research participation” \(^{187}\). Of course, this view also raises serious concerns, not the least of which is the risk of reducing national identity to genetics, a negative manifestation of genetic exceptionalism. The risks of doing so made headlines in 2009, when the United Kingdom border agency proposed using isotope analysis and DNA testing to determine the nationality of asylum seekers, in their “Human Provenance Pilot Project” \(^ {456}\). In June 2011, it was reported that United Kingdom border agency would cancel the project after reportedly spending £190,000 on a pilot project (see: http://news.sciencemag.org/scienceinsider/2011/06/uk-abandons-study-of-
nationality.html?rss=1). In another example, two studies reported in 2010, ignited a debate over Jewish ancestry and the notion of a biological Jewish identity. Keeping in mind, that it is in fact impossible to identify an individual as being from a specific country on the basis of their DNA, it clearly remains a serious concern. Both within and between countries, as there are implications for those who both fit the national genetic profile as well as those who may not. Benjamin (2009) has criticized genomic sovereignty specifically on this basis. She pointed out that genomic sovereignty is a blatant attempt by countries to brand and market their ‘national’ populations (either based on diversity, admixture or heterogeneity). She also argued that it risks reducing citizenry to a biological component; an act that results in scientific citizenship where the population is the resource, and potentially property.

6.5.3 Genomic Sovereignty as Patrimony

An analysis of the data indicates that the concept of genomic sovereignty is linked to ‘patrimony’. Rabinow (1999) wrote in his book, French DNA that, “as early as 1794, patrimony was lexically opposed to vandalism” and suggested that term ‘genetic patrimony’ embodies the bioethical concepts of menace, integrity, dignity and identity alongside a duty of protection in a pastoral sense. Similarly, here, genomic sovereignty also displays protective connotations and seems intended as a method to shield local populations from bio-exploitation. Although similar to both the economic and heritage argument, it goes beyond them, in that its benefits are not purely economic and it does not only refer to culture. Patrimony, it has been argued, links both the concepts of property and being – both incorporate value, but towards different ends. Indeed, many of the interviewees in my studies mentioned the importance of regulating access to ensure that local needs and priorities are being met. The following statement best highlights this:
“...we believe that if we do not carry out studies to really understand our genomic patrimony that we possess, well no one else will because they will be interested in their own populations, secondly, should the interest exist and they (other countries) come to get this information, they make us dependent on this information and then it will cost us...we have to develop our own genomic information.”

The feature of patrimony was best demonstrated by INMEGEN in Mexico, who considered their approach to mapping their indigenous population as less exploitative than past attempts of ‘safari research’ by scientists from the developed world. Key informants stressed the importance of gaining the trust of Mexico’s indigenous populations as they conducted the initial baseline variation project, towards the long-term goal of delivering public health genomics, a priority for INMEGEN and the Mexican government. Still, it is also important to recognize that at the same time, the interests of state governments and indigenous peoples may diverge as already demonstrated, indicating the need for extensive dialogue between the two, an approach which has so far eluded the CBD, where indigenous peoples have requested to be considered as ‘Parties’ as opposed to stakeholders.

Together, these three features of genomic sovereignty are complementary to those features I have already examined in the previous section. This analysis however broadens the scope and the significance of sovereignty as a foundation on which to explore contemporary debates on ownership of- and access to- human genetic materials. For example, as I have already indicated, the CBD recognizes sovereign rights over genetic resources in an effort to prevent bio-piracy and ensure equitable access to the benefits from a nation’s plant and animal genetic resources. The goal of ensuring equitable access to benefits was also specifically demonstrated by the Indonesian government, when they withheld their H5N1 human samples in a bid to ensure
the development and implementation of access frameworks. It is however, not entirely clear that exerting state sovereignty is the only means to achieve these goals – as the CBD incorporates benefit sharing as an additional requirement of the treaty and not as a feature of state sovereignty. Whereas, in the analysis I have described here, genomic sovereignty is primarily employed to ensure that developing countries are able to capture the value of these locally led, early-stage investments in genotyping initiatives. I would thus propose that genomic sovereignty has been an essential element towards encouraging local capacity building and protecting early-stage local capacity investments in human genomic research by establishing trust through governance and oversight. These findings reflect work by Upshur and colleagues (2007) who have pointed out that when human tissues are exported from the developing world, there is little investment in the local infrastructure and capacity building needed to improve local health research. Indeed, it has been reported that over the years, Uganda has lost out on significant investment in the health research sector due to the export of tissues collected in Uganda by foreign researchers (at one time 80 percent of all tissue was exported). Of course, as part of a circular argument, the reasons that the tissue had been exported in the first place had to do with the lack of critical infrastructure in Uganda. More recently, as growing evidence of the strength of the bio-economy, a 2011 report entitled, ‘Economic Impact of the Human Genome Project’, found that this investment generated a $796 billion and created 310,000 jobs in the U.S. This is not a minor economic benefit.

In the future, these aspects of the definition will need to be teased out, as understanding how genomic sovereignty is conceived and the qualifications that have been added will need to be complete. These initial empirical analyses and observations that I have provided will contribute to this goal.
6.6 Discussion

In the previous sections, I have described the principles and limitations of state sovereignty and examined how it has been linked to the field of genomics over the past twenty years or so. I have also provided an in-depth analysis of the themes genomic sovereignty, generated from a cross-comparison of several case studies. In the following section I will explore how the principles of sovereignty (authority, territoriality, mutuality and non-intervention) fit with the concept of genomic sovereignty. Throughout, I will draw from Schrijver’s (2000) ‘sovereignty test’, developed from the perspective of international law, as highlighted in Table 2, in an effort to examine the practicality of the concept. Granted, there are no international laws regarding human genetic material, regardless it is still useful to consider it from this perspective. Predominantly this is because of the global nature of large-scale human genomic research and the emphasis placed on international cooperation by the various stakeholders. Indeed, as stated within the UN Millennium Project *Innovation: applying knowledge in development*, “[M]ost issues of science, technology, and innovation now cross lines of national sovereignty. Science and technology had already become a truly international activity in the twentieth century, with huge increases in transnational collaboration on science, technology and innovation issues” 28. Of course these statements must also be balanced with the belief that the Mertonian norms of science (universalism, disinterestedness, communalism and organized skepticism), where scientists may consider themselves beyond the considerations of national sovereignty. However, as I have already outlined, by virtue of the bio-economy, science is also increasingly a national enterprise to generate and further economic competitiveness. Thus, I would argue that science is increasingly politically driven, involving a state role in generating mechanisms and tools to both protect and encourage scientific investment and where as Mallard and Paradeise (2009) have stated “the products of science have come to be identified as essential national assets” 209.
First, *authority*, in the case of genomic sovereignty, is not straightforward. As I have already shown, there is a smattering of existing national legislation and no international legislation that recognizes state sovereignty over human genetic material. At the international level human genomic research is increasingly influenced by epistemic communities of research scientists, international agendas and philanthropic funding agencies through guidelines and recommendations. A feature of globalization, these non-state actors have, at the very least, reduced the role of the state in large-scale human genomic research. Oftentimes, these groups view the state as a limiting factor in achieving their goals (e.g.: international cooperation). For instance, some scientists have raised concerns regarding the CBD, which is meant to facilitate access by allowing for sovereignty over genetic resources. They have accused the CBD of stifling access through complex bureaucratic procedures, broad generalizations and the criminalization of scientists\(^{356,462-465}\). On the other hand, despite an increase in these influential non-state actors in the international arena, it has also been argued that the state continues to be the dominant actor\(^{55,404}\). Particularly as the state is commonly the only recognized and legitimate unit at the international level, able to both implement and monitor legislation. Still, in order to achieve consensus on legislation, the state will increasingly need to include non-state actors to ensure “representativeness and legitimacy (...) for international decision-making.”\(^{404}\)

A push for state sovereignty over human genetic materials however, in some cases, will diverge from indigenous peoples’ internationally recognized right to self-determination and sovereign control. As pointed out by Barkin (1994) and evidenced by the CBD, it is difficult at best to satisfy the demands of the established state and nationalist or individual claims\(^{399}\). However, recent advances in research guidelines with indigenous communities\(^{444}\) demonstrate that such a
task is possible. Moreover, INMEGEN in Mexico may provide important lessons. As I outlined earlier, Mexico has established legal jurisdiction over human genetic materials. Those we interviewed held the opinion that the ‘genomic sovereignty’ legislation, together with extensive community consultations with indigenous groups, provided INMEGEN with legitimacy and generating the trust necessary to encourage Mexico’s indigenous peoples to participate in INMEGEN’s Mexican HapMap Project. Of course, these examples are limited and additional appeals may come from less recognized, but equally persistent groups (e.g.: disease-based). Without existing authority, these scenarios can and will raise simple dilemmas, such as who should a foreign researcher consult when choosing to obtain genetic materials from a specific group, state government, indigenous representatives or both. What about more complicated potential future dilemmas such as internationally led on-line disease-based communities.

In both instances, state sovereignty that also incorporates universal values as described by Schrijver (2000)\textsuperscript{404}, could advance efforts towards developing consensus on human genetic material. It is admittedly unlikely that there will ever be full consensus at the international level on ethical issues in the field of human genomic research, but this should not engender inaction. The CBD, as the only true example of an internationally and legally binding recognition of state sovereignty over genetic resources, is influenced by shared values that aim to preserve biodiversity, respect human rights and ensure fair and equal access to the benefits of biodiversity. One could argue that human genomics research has been influenced by the universal values, as they are described in the various international guidelines and recommendations issued by HUGO, the OECD and UNESCO. These guidelines (e.g. global public goods, etc.) can provide a starting point for both national legislation and international guidelines that recognize sovereignty over human genetic materials. Those statements though, that frame the human genome as the common heritage of mankind are inconsistent with paradigm of state sovereignty over human
genetic materials and would require a slight shift. A repositioning that may be considered
difficult by some, still as already pointed out by others the stance is generally considered
rhetorical \(^{393}\), applies for the most part to the human genome symbolically \(^{191}\), and when applied
to commercialization and benefit sharing frameworks, lacks practicality \(^{394}\).

Second, as demonstrated by the hesitancy of the U.S. to sign the CBD, the scope of state
sovereignty over human genetic resources, or *territoriality* needs to be clear. Territoriality, the
recognition of which is the basis of international relations \(^{400}\), refers to geographic boundaries
(e.g.: a country) and can also be linked to ownership and property \(^{405,413}\). Indeed, some have
argued \(^{413}\) that sovereignty can only be understood in terms of property rights, which allocate
material resources through the mechanism of legal rules established by the state \(^{405,413}\). For many,
this may pose the most significant challenge to recognizing sovereignty over human genetic
material. Can the state ‘own’ human genetic material as property, and does such a position
stretch the role of state sovereignty beyond what can be considered reasonable? Obvious
concerns have been raised regarding scientific citizenship and bio-value \(^{455,466}\) and bio-politics as
described by Foucault (2008) \(^{467}\), Agamben (1998) \(^{468}\) and Esposito (1998) \(^{469}\) where sovereign
states determine the value or non-value of human life. A phenomenon, which Agamben (1998)
has suggested is the result of the “synthesis between biology and economy” \(^{468}\).

Genomic sovereignty however, need not imply ownership by the state. Sand (2004) has argued
that in an era where common pool resources (e.g. seabeds and plant genetic resources) are being
bounded by national sovereignty in international treaties, stewardship, not proprietorship, is the
intended goal \(^{470}\). Such a model, wrote Sand (2004) is the public trust doctrine (PTD) \(^{470}\), which
requires that state governments make the trust available to the general public for use, although
this is not the only permissible use (e.g. licenses can be made available for a fee); the trust cannot
be sold, and; the trust must be maintained for public use. The PTD assigns both an authority and a duty to the trustee with respect to the trust. Moreover, it can be argued that it applies to current as well as future generations, implies public participation, as stakeholders can “hold the government accountable” and encourages sustainable and “equitable sharing” of the trust.

These features of the PTD are not in conflict with sovereignty over natural resources. Where the UN General Assembly recognizes duties of development and co-operation, “the rights of peoples and nations to permanent sovereignty over their natural wealth and resources must be exercised in the interest of their national development and of the well being of the people of the state concerned”. An important question, which will need to be answered in the future, is what are these duties of development. For instance, should states be required to fund and maintain large-scale genetic databases or are they only required to implement legislation that facilitates licensing of human genetic materials?

Knoppers (2007) criticism of national legislation was that it failed to account for the need for large-scale genetic databases to collaborate and network. Moreover, my research has shown that in many developing countries, international collaboration with developed world scientists is necessary to gain access to infrastructure and/or funding. In these cases sovereign legislation would be akin to a balancing act. Indeed, many interviewees I spoke with believed that these realities compromise a country’s ability to legislate regarding their human genetic resources. However, although international cooperation may appear to conflict with the concept of sovereignty, Schrijver has argued that the duty of cooperation can instead act as a pillar to sovereignty. He has pointed out that it can underpin the movement in international law to strengthen the strategic position of developing countries in response to the intensifying exploitation of their resources by other states and foreign multinationals. Given my earlier analysis of genomic sovereignty, I would argue that this is directly applicable to human genetic
materials. Amongst those participants I interviewed, the majority considered human genomic research to be a global enterprise. The participants in this study also expressed a desire for the knowledge generated to remain in the public domain. There is also empirical evidence that demonstrates Schrijver’s argument. For instance, both INMEGEN and the IGVdb, countries with jurisdictional guidelines and legislation, have since made their genetic databases available in the public domain and are participating in international collaborations, providing evidence that sovereign legislation need not impede these relationships. In addition, the HUGO Pan Asia Consortium provides a valuable model for consideration, where international collaborative efforts between scientific groups from various geo-political environments with varying degrees of scientific infrastructure assumed and respected each country’s stewardship over their genetic materials\textsuperscript{17,340}. The lessons learned by this consortium may prove useful to others, including the recently launched H3 Africa project (see: http://h3africa.org/).

The idea that human genetic material be placed in the public trust is not novel. Initially it was proposed by Gottlieb (1998)\textsuperscript{211} and later developed by Winickoff and colleagues (2003) who suggested a charitable trust model for genomic biobanks\textsuperscript{140} and further developed into a tissue trust model for the developing world by Emerson and colleagues (2011)\textsuperscript{212}. In addition, a “global genome trust” was also proposed by Looney (1994)\textsuperscript{474}. In each of these proposals, a third party custodian (e.g.: a board of trustees made up of stakeholders) of the non-profit trust acts as a moderator between the participants and the researchers at the project, regional or national level. The UK Biobank provides somewhat of a model of this approach, though it does so in a paradoxical fashion as while considering itself a ‘steward’ it also claims ownership over
the resource along with all of the rights of ownership \(^{145}\). There is also empirical support for the model, as various stakeholders have contended that it mitigates the ‘ownership’ dilemma and facilitates the exchange of human genetic materials \(^{95}\). Trust models however, at the project level, are at risk of being too informal and could lack transparency, depending on the context and the parties involved. For instance, a trust model initiated by a private pharmaceutical firm may only generate confidential ‘agreements in principle’, that have little recourse for those involved and lack legal legitimacy. The Avesthagen database was initially proposed to the Parsi community as a not-for-profit trust, but was ultimately rejected for a number of reasons related to bureaucracy and trust. During several informal discussions I had with various stakeholders in India, they expressed concerns regarding the transparency of such an endeavour where there is no legal recourse at the state level.

Ossorio (2007) has previously deliberated the application of public trusteeship over human genetic materials, but found the concept wanting, in that “the resource resides in the bodies of all people” raising the dilemma of individual autonomy and “human genetic material is a resource that transcends state and national boundaries” where there is little consensus on moral and commercial aspects of human genomic research \(^{192}\). Moreover, there is the concern of ensuring sustainable funding for these initiatives \(^{140,212}\). Admittedly, these are genuine concerns, but Iceland and the HSD and Biobank Act provide important practical lessons on this. All data held under the HSD is considered a common resource of the Icelandic nation and the role of the Icelandic government is as the steward over these materials \(^{104}\). Similarly, in the Icelandic

\(^{xxxiv}\) As per the UK Biobank Ltd. Ethics and Governance Framework “UK Biobank Limited will be the legal owner of the database and the sample collection (...). Such ownership conveys certain rights (...). Participants will not have property rights in the samples. (...) UK Biobank will serve as the steward of the resource, maintaining and building it for the public good in accordance with its purpose” \(^{145}\).
**Biobanks Act**, biobanks are licensed to applicants, who can be either public or private institutions, and human genetic material cannot be ‘owned’ by a licensee. However, the approach to human genetic materials in Iceland has been compared to their approach to another ‘national common resource’, the fisheries, raising some criticisms regarding the commodification of common resources as licensees pay for access (initially for DeCODE, this was for exclusive commercialization). This may be true but the PTD still provides a reasonable alternative to exposing human genetic materials to a pure market system. In addition, as with above, one could argue that there is an additional duty present here, related to public health genomics. The agreement between deCODE and the Iceland government was that in return for exclusive access, deCODE would return 6 percent of the profits to the Icelandic government to be invested in health care. Exclusive licensing was criticized as per above and should be avoided. Public access to the resource as per the PTD model should be encouraged and licensing fees accounted for on a sliding scale that recognizes the spectrum of not-for-profit research scientists to private industry. Admittedly, this is not always clear and has been one of the more significant challenges faced by the CBD, still it provides a reasonable alternative. Ideally, licensing fees can then be reinvested back into the health care. Again, Mexico provides an excellent model here, as INMEGEN is incorporated within the National Institutes of Health with a mandate for public health genomics.

Although the public trustee doctrine is not complementary to ‘common heritage of mankind’, it is with the notion of global public goods – approaches that are increasingly incorporated into the international recommendations on human genomic research. As I have already highlighted in the literature review, these goods require ‘shared meaning’ and ‘cooperation’ to address the limitations, which arise (free rider problem and the prisoner dilemma); both of which could be incorporated into an international treaty similar to the CBD but which would require an
international mediating body (e.g.: UN). Sovereign authority can resolve the dilemma of who is responsible for providing access goods and facilitating collaboration: the state. In addition, I have shown that the public trustee doctrine provides a reasonable and practical alternative to exposing human genetic materials and information to a pure market system. It can also provide a framework in which states can incorporate the ethical, legal and social implications of human genetic research.

Finally, to date sovereignty over human genetic resources is not necessarily mutually recognized by other states. This is not the case with non-human genetic resources, such as with the CBD, where a signed international treaty recognizes the state right to sovereignty over non-human genetic resources and thus guarantees mutuality and non-intervention between those who sign at the level of international law. Still, not all states have signed the treaty, namely the United States, a country that has significant investments in human genomic research and is considered a dominant international player and a global leader. Of course, mutual recognition need not always be recognized through the existence of a signed treaty; sometimes it is implicitly recognized as the “exchange of roughly equivalent values”\(^4\). However, in the case of human genetic materials, it is unlikely that there is, or ever will be, such an exchange and instead mutuality may be better framed as ensuring justice, through an international agreement on principles of stewardship and sovereignty, which also admits to a “hierarchy among states”\(^4\) and the risk that human genetic materials become a ‘club good’. Chadwick and Strange (2009)\(^2\) have suggested that harmonization of ethics and governance in human genomic research is “indeed necessary but not as an end point – rather as an ongoing process”\(^2\). I would agree as my analysis indicates that genomic sovereignty is part of an attempt by these countries to establish and protect nascent capacity and infrastructure in human genomic sciences in the developing world. Thus, there is every reason to believe that genomic sovereignty could evolve to account
for novel and unexpected governance issues associated with human genetic material or even that it may become irrelevant.

6.7 Conclusion

The aim of this chapter has been to set out the scope and significance of state sovereignty as a foundation on which to explore contemporary debates on human genetic materials. Table 3 provides a summary of my analysis of genomic sovereignty (see below). It links the principles of sovereignty with some of the challenges that I have outlined and my proposed recommendations for genomic sovereignty.

Table 4: Summary and Recommendations on Genomic Sovereignty

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Currently, there exists a gap regarding legislation on ownership and access of human genetic materials in large-scale human genomic research. At the international level there are several
recommendations that are not legally enforceable and do not have clear mandates to develop international norms and standards for collaboration in genomic research. Alternatively, some countries have also chosen to establish jurisdictional legislation over human genetic materials, still these national laws are not harmonized and often fail to address the important need to cooperate in large-scale human genomic research. This gap has presented several challenges, one of these being the perceived inequality between the North and the South, in large-scale human genomic research, where the developed countries are seen as taking advantage of lesser-developed countries that are rich in human genetic materials (e.g.: African countries). For instance, Miles (2006) has argued that human genomic sciences in developing countries may result in ‘bio-colonialism’ or ‘genetic piracy’ of human genetic materials in developing countries that do not have the resources to carry out the research themselves ⁸. In this chapter I have examined the relationship between sovereignty and genetics and provided an in depth analysis of genomic sovereignty in the developing world. I have shown that genomic sovereignty is based in economic, patrimonial and public support arguments. I have also demonstrated that genomic sovereignty over human genetic materials is justified and provided recommendations for how it may be best conceptualized. I have not argued that genomic sovereignty is necessary. However, it is possible to do so given the lack of global consensus on ownership of- and access to- human genetic research, the increasingly complex and global nature of large-scale human genomic research and the possibility that individuals and groups will respond to these issues through the court system (e.g the Havasupai nation and the Myriad case).

I would argue that an international treaty or agreement that recognizes sovereignty over human genetic materials framed within the public trust doctrine can provide an appropriate framework for addressing ownership and access concerns at both the national and international level. At the national level, genomic sovereignty can provide an appropriate framework for those individuals...
conducting large-scale genotyping research within the country. At the most basic level, jurisdic- 
tional law over human genetic materials recognizing the state as steward can encourage 
investment in local infrastructure and capacity. Sovereignty over human genetic materials framed as a fiduciary duty also encourages public participation, as stakeholders can “hold the 
government accountable” and encourage sustainable and “equitable sharing” of the trust 472.

Indeed in the age of globalization, to be successful, a country can only ensure representativeness and legitimacy by incorporating the interests of non-state actors while also balancing the overall welfare of its citizens. Increasingly, there is precedence for how this can be achieved (e.g.: CIHR Research Guidelines). Moreover, at the international level, contrary to common perception, it can provide an effective and practical framework for international cooperation in large-scale genomics research. An international agreement on sovereignty over human genetic resources can eliminate contradictions, facilitate access to human genetic materials, and “ensure fairer distribution of benefits” 465. By involving international non-state actors, genomic sovereignty need not be as cumbersome as the Convention on Biological Diversity; at the very least it will not be as inefficient as the common heritage of humanity. Still, any attempts to establish genomic sovereignty legislation will require careful consideration of the implications (e.g.: genetic exceptionalism, scientific citizenry etc.) as well as reflection on the obligations of the state.
Chapter 7
The next steps for genomic medicine – challenges and opportunities for the developing world

This chapter is an updated version of a paper that has been peer-reviewed and published in Nature Reviews Genetics with the following citation: Hardy B., Séguin B., Goodsaid, F., Jimenez-Sanchez, Gerardo, Singer PA., Daar AS. (2008) The next steps for genomic medicine: challenges and opportunities for the developing world. Nature Reviews Genetics. 9(10):s23-s27

As lead author, I was responsible for writing the paper. Listed co-authors contributed to the initial conceptualization of the larger project, facilitated access to participants and provided essential comments throughout the drafting of the publication. Updates to the chapter were made to account for recent advances in human genomic variation studies and to incorporate results from chapter 6 of this dissertation.

7.1 Introduction

Due to rapid economic development, in 2010 emerging and developing economies grew by 7.2% in comparison to 3% in advanced economies and have generated two thirds of global economic growth over the past two years. Emerging economies in the developing world such as India, China and Brazil have been investing heavily in innovative science and technology (S&T), establishing infrastructure and making significant progress in the life sciences arena. The situation in the poorer parts of the developing world, especially in sub-Saharan Africa, has so far been different. There continues to be little significant expenditure on research and development (R&D): expenditure on R&D in sub-Saharan Africa is less than 1% of GDP and in sub-Saharan Africa total health expenditure as a percentage of GDP in 2009 was 6

...
compared to 16.2 in the United States (US) \(^{482}\). However, in terms of understanding the value of S&T for development, investing in S&T, and realizing the need to spend more on health, the situation may be changing \(^{483-489}\). In 2006, African Union countries endorsed the call to spend 1\% of their GDP on S&T and pledged to spend more on health (see: http://www.africa-union.org/root/au/Documents/Decisions/com/AU6th_ord_Council_Decisions_Jan2006_Khartoum.pdf; http://belfercenter.ksg.harvard.edu/publication/17382/freedom_to_innovate.html). And in recent years, Malawi, South Africa, Rwanda and Uganda have surpassed this goal \(^{484,490}\).

The first part of this dissertation described two case studies in India and South Africa, which have demonstrated the successes and the challenges of emerging economies in the developing world that are investing in large-scale human genomic variation studies. Together these findings were part of a larger research project (described in chapter 1) looking at initiatives in Mexico, Thailand, and HUGO Pan-Asia (See Appendix 1 for the series of publications). A cross-comparison of these case studies generated several themes: the need for political will and institutional leadership; gaining entrance into the knowledge-based economy; addressing local health needs; and genomic sovereignty (see Table 1 in chapter 6). These themes are interrelated and provide a potential roadmap for countries in the developing world looking to invest in human genomic sciences \(^{17}\). Investments into science and technology (S&T) are a critical first step to establishing infrastructure and capacity in human genomic sciences. In the long run, these investments will enable these countries to embark on the path to the medical and health applications of genomics, and to benefit economically. Indeed, it is now estimated that the $3.8 billion invested into the Human Genome Project generated 310,000 jobs and $796 billion in economic benefits in the U.S. \(^{461}\). For those countries, like those featured here and Brazil and China, that have already embarked on major genomics initiatives, establishing research institutes and conducting the research are the first steps on the path to genomic medicine. For them the
major question now is how they will go from this early phase investment towards the hoped-for health-oriented applications, and economic benefits. For others that have not started, the question is: what are the potential entry points? And for all developing countries, with or without current genomics initiatives, the question is: what are the challenges and opportunities along the way to the adoption of genomic medicine and deriving economic benefit from genomics? Some challenges are common to all countries, whether economically developed or developing. Other challenges will be more specific to developing countries. Here I will present perspectives on the challenges and opportunities associated with the adoption of genomic medicine, particularly in the developing world, and the need to understand the interdependent nature of efforts to develop genomic medicine.

7.2 Genomic Medicine in the Developing World

The case studies in India, Mexico, South Africa, Thailand and HUGO Pan Asia are no longer the only projects of their kind, taking place in emerging economies and the developing world. As I highlighted in the review, China was the only developing country that participated in the sequencing of the human genome. A decade on, it has a number of important initiatives related to genomics. For example, in 2008, China’s Beijing Institute of Genomics (BGI) (http://www.big.ac.cn/big/english/index.jsp) released a diploid genome sequence of an Asian individual. This sequence was the first stage of their Yanhuang Project in which they plan to sequence 100 Chinese genomes (http://www.genomics.cn/en/research.php?type=show&id=134). And, on June 18, 2011, the Chinese government announced the creation of a national gene bank in Shenzhen with BGI. In a nod to genomic sovereignty, Mr. Chengyuan, head of the high-tech industry department of the National Development and Reform Committee said, “China will be able to better protect, research and utilize its precious genetic resources, boosting the genetic
industry and *safeguarding the country’s genetic information*” (see: http://news.xinhuanet.com/english2010/china/2011-06/18/c_13936519.htm). Moreover, since the publication of the South Africa case study in 2008, there have been a handful of exciting developments in human genomic sciences across Africa. In 2008, a locally led bio-bank and pharmacogenetics database was established in Harare, Zimbabwe containing 1,488 samples from several ethnic sub-Saharan African populations (Nigeria, Kenya, Tanzania, Zimbabwe and South Africa)\(^\text{382}\). At the time, the “biobank represent[ed] a significant contribution to the efforts to jump-start pharmacogenetic and genomics research in African populations”\(^\text{382}\). Then, in late June 2010 the NIH and the Wellcome Trust announced the Human Heredity and Health in Africa (H3 Africa) project (http://www.genome.gov/27540084). A five-year, multi-million dollar investment in African researchers, on African soil to investigate genetic, clinical and epidemiological patterns across Africa (see: http://h3africa.org/). The initial seed for the idea was planted during the 2007 African Society of Human Genetics meeting in Cairo, Egypt and framed as a project that would contribute to reducing the genomic divide\(^\text{492}\). Second, in January 2011, the Southern African Society for Human Genetics announced the launch of a Southern African Human Genome Programme, intended to, develop capacity for genomic research in southern Africa; establish a sustainable resource for genomic research (including a regional sample repository and database); and, translate the information and knowledge into improvements in human health\(^\text{453}\). Those involved in the Southern African Human Genome Programme project are advocates of genomic sovereignty and are lobbying to have legislation established in South Africa\(^\text{214,453}\). Finally, in June 2011, the Centre for Proteomic & Genomic Research announced a partnership between the Division of Human Genetics at the University of Cape Town and
PGENI, establishing a regional PGEND Center of Excellence “to map traits underlying the efficacy of drug treatments in Southern African populations. These investments in sub-Saharan Africa, particularly South Africa, do not reflect an about face in political will, but instead sheer determination by local and foreign stakeholders who have recognized the critical need to initiate scientific infrastructure and build capacity in human genomic sciences in sub-Saharan Africa through local and international partnerships. This is a feature which Wonkam and colleagues (2010) have argued will be critical to their success.

For all that, there remain those critical of these investments. Following the publication of the India and South Africa case studies, at a HUGO conference in Hyderabad, some critics argued that India and others should “re-prioritize their genetic goals”, they held that India and others were placing too much priority on genomics and common complex diseases and not enough on infectious and single gene disorders. First, I agree that these criticisms are valid and clearly investments and aims in human genomic sciences in developing countries will need to be prioritized at a level that is context-specific. Coloma and Harris (2009), for instance, have written that lesser developed nations planning to invest in genomics “should start by establishing their priorities”, suggesting as an example, that resource limited countries explore opportunities in molecular genomic approaches to infectious diseases. Either way, as recommended by the WHO countries in the developing world, sooner rather than later, need to invest in infrastructure and capacity for human genomic sciences, through collaborations if necessary, particularly as demonstrated by H3 Africa and HUGO Pan Asia. Second, infectious and single gene disorders are no longer the only health challenges in developing countries. At a conference

xxxv Email announcement received from the director of CPGR on June 17, 2011
on Emerging issues in Regulatory Medicine in Mexico, then Health Minister, Julio Frenk highlighted that as Mexico has developed, its epidemiological patterns have changed; it has less infectious diseases, an aging population and an increase in chronic disease. These statements also hold true for India, China and South Africa. Moreover, there is a growing trend of common chronic disease across the entire developing world, which has largely been ignored by the developed world.

Thus, on the contrary, the case study of India (as well as those of Mexico and Thailand) demonstrates that these initiatives are linking their efforts to local health needs; and that this is key to their current success. It is well known that establishing infrastructure and building capacity health research in developing countries is necessary to “improve health systems and attain better health”. The research featured in this dissertation further confirms that waiting for technologies to be developed and then subsequently transferred and adapted for the developing world is increasingly irrelevant; instead locally led initiatives through pooled resources or equitable partnerships (both South-South and North-South) are the future.

7.3 Exploring Potential Opportunities

Countries in the developed world, such as the United Kingdom, the United States and Japan have made tremendous investments in R&D towards genomic medicine. Emerging economies in the developing world that have made a similar commitment will need to consider how to best identify their next steps into genomic medicine. Thinking of these next steps may also help them identify unique niches that would give them commercial advantages. For other countries that have not yet started genomics initiatives, their entry points will depend, to some degree, on their respective life sciences innovation infrastructure. Such entry points would need
to be appropriate for their level of investment in R&D in genomics and in the existing health care delivery systems.

The current trend in terms of both next steps and entry points is for countries in the developing world to collaborate in R&D with more developed nations (North-South collaborations). The HUGO Pan Asian SNP Consortium provides an example of North-South R&D collaboration between Asian countries. Lessons learned from such collaborations have contributed to the further development of international ethical guidelines for benefit sharing, ownership and R&D capacity-building in human genomic research. However, increasingly there is a trend towards South-South collaborations ([http://www.scidev.net/en/science-and-innovation-policy/south-south-cooperation/policy-briefs/opportunities-and-challenges-in-south-south-collab.html](http://www.scidev.net/en/science-and-innovation-policy/south-south-cooperation/policy-briefs/opportunities-and-challenges-in-south-south-collab.html)) in which developing countries pool their limited resources, help each other and learn from each other’s experience. Similarly, Mexico’s significant investment in genomic research infrastructure provides other Latin-American countries lacking genomic R&D capacity the opportunity to pool their resources with Mexico, as opposed to the US or Europe, towards the development of genomic medicine and innovative genomic medicine products for this region.

Next step and entry points will need to be cost-effective. Pharmacogenomic approaches, including diagnostics, can reduce adverse drug reactions in countries that can least afford to waste money on drugs, which may not have the expected therapeutic effect. Diagnostics may be easier to develop than new drugs and vaccines as they bypass the costly clinical trial stage and tend to have a shorter regulatory review schedule. In this respect, once the cost drops significantly, pharmacogenomic diagnostics may be an early next step or even entry point for some developing countries. Given their access to large populations exposed to multiple
infections (HIV/AIDS, Malaria and TB), another viable option for developing countries could be to focus genomics R&D on the host-pathogen responses for these infections.

Bioinformatics provides another potential option. The South Africa National Bioinformatics Institute (SANBI) (http://www.sanbi.ac.za/), for example, has developed eVOC a software program that unifies gene expression data by facilitating a link between the genome sequence and expression phenotype information (http://www.evoontology.org/)\(^{498}\). The World Health Organization-based Special Program on Tropical Diseases Research and Training runs training programs on bioinformatics for scientists in the developing world\(^{499}\). More recently, in the private sphere, an Indian software firm, Optra Systems, conceptualized and built the genomics database for Stanford University’s genome variation database\(^{500}\).

National genotyping projects are useful for establishing baseline profiles, which may have great benefit for subsequent studies. For example, INMEGEN has revealed significant ancestral components between populations from different regions of Mexico. Moreover, identification of unique SNPs and significant differences of functional variations related to drug metabolism suggest the need for regional approaches for the study and applications of genomic medicine in Mexico (personal communication). The Indian Genome Variation Consortium has uncovered high levels of genetic divergence between groups of Indian populations that cluster largely on the basis of ethnicity and language\(^{15}\). The study of such population groups will be useful for addressing stratification and complex study design issues\(^{15}\). Here, large collaborative efforts on R&D in fields such as pharmacogenomics, vaccinogenomics and toxicogenomics could serve as entry points for developing countries. Examples include pharmacovigilance programs and detailed analyses of data from vaccine trials in which some but not all the human subjects respond to a particular vaccine; researchers have emphasized the importance of human
genomic sciences to the design of effective vaccines for emerging infectious disease on the basis of variation host immune response\textsuperscript{501}. A well-known classic example demonstrating that genetic factors may have a strong effect on the immune response to certain vaccines is the response to hepatitis B surface antigen (HBsAg). Upto 10% of people do not respond to HBsAg vaccination. The unresponsiveness is associated with HLA antigens coded for by genes in the major histocompatibility complex (MHC). Recent evidence in fact suggests that although genes encoded within the MHC are important for this immune unresponsiveness, more than half the heritability is determined outside this complex. Identification of these genes will help us to understand regulation of immune responses to viral proteins\textsuperscript{502}.

The potential to improve the understanding of genomics and traditional medicines through fields such as nutrigenomics provides another possible entry point that offers these countries an intellectual property advantage. Traditional medicine is well established in China and India, where a memorandum has been signed to further the understanding of their respective traditional medicine sectors (http://economictimes.indiatimes.com/News/News_By_Industry/Healthcare\_Biotech/Healthcare/India\_China_to\_step\_up\_cooperation\_in\_traditional\_medicine/rssarticleshow/3210228.cms). Since publishing the case study on the Indian Genome Variation Consortium, members of the Indian Genome Variation Consortium have demonstrated links between India’s traditional medicine, Ayurveda, and the genome\textsuperscript{503,504}. These studies indicate that Ayurveda principles may be effective at identifying underlying biomarkers that confer differences in disease risk in India\textsuperscript{503}.

Although limited, private sector firms in developing countries have also begun to leverage the opportunities in genomic medicine, identifying possible entry points and employing unique
resources. Avesthagen Ltd (www.avesthagen.com), an Indian-owned life-sciences company, has a large-scale genotyping project of the Parsi population in India\textsuperscript{505}. They predict an initial market in translational medicine such as genomic medicine with an eventual foray into early diagnosis, pre-symptomatic and lifetime treatment through a combined offering of wellness products (e.g.: nutrigenomics) and personalized healthcare. In March 2011, in a continuation of their commitment to investing in the commercialization of human genomic sciences, they announced a commercial whole genome sequencing service (http://www.avesthagen.com/docs/PR220311.pdf). While in South Africa and Thailand a few innovative firms are targeting the medical tourism market\textsuperscript{338,339}.

Finally, additional possible entry points might involve anthropology or human history and migration studies, as part of establishing a baseline of data for possible health applications. This, for example, was the original impetus for the HUGO Pan-Asian SNP Consortium\textsuperscript{151}. Other countries may become involved as a result of participating in the Human Genome Project and the HapMap project, as did Nigeria and China\textsuperscript{30,64,68}.

7.4 Challenges

Genomic research platforms in emerging economies and developing countries will be faced by a number of similar challenges as they become established and proceed towards the adoption of genomic medicine in their respective countries. My cross-comparative analysis of the case studies featured in this dissertation revealed several challenges faced by these countries. These are summarized in Table 1 (see below).

| Table 1: Challenges faced by developing countries investing in genomic medicine |
A number of these challenges are local and can be addressed as such by and in individual countries. Others, such as establishing international R&D collaborations in genomics research and the need to address the lack of harmonized regulatory infrastructure for genomic medicine, require collaborative efforts on an international scale to address them.

Internationally, issues that rapidly need to be addressed for productive and equitable collaborations include data and sample sharing, research capacity building in developing countries, and rules and guidelines for building and using international repositories containing long-term treatment outcomes in both developed and developing nations. These issues are often not straightforward to address. For example, data and sample sharing in many developed countries have traditionally focused upon consent and the concerns associated with privacy and confidentiality. But in international collaborations, in addition to these concerns, considerations will also have to be given to the sovereign nature of the data and samples sourced.

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<th>International Challenges</th>
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<td>Access to skilled human resources</td>
<td>Establishing international research and development guidelines for collaborations in human genomics research</td>
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<td>Ensuring sustainable funding and political will</td>
<td>- Data sharing</td>
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<td>Securing alternative funding</td>
<td>- Research capacity building in developing Countries</td>
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<td>Improving collaborations within- and between the public research sector and the private sector</td>
<td>- Rules and guidelines for building and using international repositories containing long-term treatment outcomes</td>
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<td>Developing opportunities for south-south and north-south collaborations</td>
<td>Addressing the lack of harmonized regulatory infrastructures for genomic medicine</td>
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<td>Developing a health-care infrastructure that can address access and delivery issues</td>
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<td>Engaging with the public to improve awareness and participations</td>
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<td>Improving the commercialization infrastructure in both the public and private sectors</td>
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in emerging economies and developing countries. This is a significant challenge, as for many stakeholders, human genomic sciences are considered a global enterprise, in which knowledge should remain public; further confirming that human genetic materials are global public goods. However, historically, in practice this has led to unsatisfactory collaborations where developed world scientists export human genetic materials from the developing world for further research and development; limiting the benefits experienced in developing countries. In these scenarios, research infrastructure and capacity are not established in the countries from which the human genetic materials originated; the materials may be patented and subsequent therapeutics unaffordable for many developing countries, and; the research conducted using the materials is not likely to be tied to the health needs of the country of origin. The case study in India demonstrated that national guidelines preventing the export of human genetic material was crucial to establishing their program; indeed those Indian researchers chose not to participate in the HapMap, primarily because it would not result in infrastructure or capacity building and that they would only be contributing human genetic materials. Genomic sovereignty however, has been criticized by those who view it as a ‘branding’ exercise by the state and have expressed concern at the idea of state ownership on the basis of bio-politics. Yet, I have showed in Chapter 6 that it need not be framed as ‘state ownership’ and can instead be considered a fiduciary duty, under the public trust doctrine. I have also demonstrated that the public-trust doctrine is complementary to the universal view that human genetic materials are global public goods and as such can provide developing countries with the capacity to prevent bio-exploitation in their countries. It is important to consider these issues early since the need for large scale collaborative research is becoming more pressing as R&D in genomic medicine advances: these studies will require data comparisons and validation in large sample sets across different populations.
Broader issues that require consideration include: the integration of genetic information into public health decision-making and guidelines for medical prioritization. Mexico’s National Institute for Genomic Medicine (INMEGEN), has described 16 a nine-point strategy for the adoption of genomic medicine, including: building an innovative organizational design; establishing the initial infrastructure; initiating nation-wide strategic alliances; conducting R&D in genomic medicine; applying genomic technology to common health problems; reaching excellence in teaching and training programs; supporting academic programs in genomic medicine; addressing ethical, social and legal issues; and translating genomic knowledge into products and services.

One of the major challenges in the application of genomic medicine in emerging economies and developing countries involves the limited, or even absent, regulatory infrastructure. These countries, in general, have limited review capacity and guidelines necessary to regulate traditional drugs and diagnostics, and for review of emerging genomic medicine products. Furthermore, regulatory capacity in many developing countries will need to encompass the work of ministries of health, science and technology, industry, commerce, natural resources, the judiciary and legislative bodies, as well as of drug licensing agencies. Developing countries may benefit from the experience of developed countries that are currently drafting the necessary guidelines to address unique emerging issues associated with the regulation of genomic medicine products 508. In the developed world, these issues are being addressed on a national scale by their regulatory agencies and on an international scale through the International Conference on Harmonization (ICH) (http://www.ich.org/LOB/media/MEDIA3383.pdf). The inclusion of emerging or developing countries in the ICH harmonization of guidelines associated with genomic medicine, as well as in other consortia that can help to improve regulatory capacity, will provide a concrete opportunity to improve the application of genomic medicine to global health.
Genomic medicine is redefining how both developed and developing countries need to work together in the application of new knowledge to improve public health. The intrinsic value of information in the human genome is associated less with national boundaries and income than with how comprehensive this information is: strongly dependent on the information from many individual genomes and from many individual countries. Data acquired from genotyping and sequencing projects in emerging and developing countries summarized above help to bridge the gaps in the application of genomic medicine between developing and developed countries. Access to these data throughout the world will be crucial for the identification of novel biomarkers of drug safety and efficacy. Whereas the generation of information from the human genome requires a global effort, its application will require development of therapeutic, diagnostic and other applications and products aimed at sub-populations and individuals. The most important benefits will likely be in the use of genomics knowledge to prevent diseases and promote health. At an individual, and perhaps sub-population level, the benefits will depend on when and how patients are exposed to medical interventions (e.g. drugs and vaccines) that are based on genomics knowledge. To achieve these aims of genomic medicine on a larger scale, public health systems in countries throughout the world need to integrate pharmacogenomic data from their citizens and to use these data effectively for the optimal allocation of diagnostic and therapeutic resources, to improve health education of their publics. Help to change their health-related behavior, educate health professionals, and re-engineer health care systems more towards prevention and health promotion.

In terms of the benefits of S&T generally, the current trend to develop knowledge, skills and products in the economically and scientifically more developed countries and then struggle to
make these available to the less scientifically developed, and poorer, countries, is not sustainable in the long run. This is why so many developing countries, especially now emerging economies, are focusing more on local innovation, invention and commercialization to break the cycle of dependency.

7.5 Conclusions

The existing initiatives in emerging economies in the developing world, which range from databases run by research networks to comprehensive national institutes with public health mandates, serve as models for how to invest in innovative S&T towards development. Such initiatives can strengthen local research infrastructure and local intellectual property regimes, address local health needs, and reduce health care costs, thus improving local health equity. How these countries choose to capture these benefits early-on will depend, in part, on the type of entry points they opt for, which in turn will depend on the level of development of their research and health infrastructure. There is much to be learnt from the experience and examples of India, Mexico, Thailand and South Africa. In 2009, Liu (2009) wrote that he “believed that these scientific advances will initiate a virtuous cycle of generating new and impactful products that can improve the human condition, and that will generate new economic opportunities. The new bio-economy will be fundamentally based on genomics, genomic reconstruction, and computational systems biology” [509].

There remain however significant challenges to be addressed prior to the adoption of genomic medicine and while, these are for the most part being experienced by all countries, these challenges are more pronounced for developing countries. There is therefore a need to strengthen existing collaborative efforts, especially south-south collaborations if these appear to be more sustainable. Current and future initiatives and investments in R&D capacity will further
enable countries in the developing world to participate as equal R&D partners with more
developed countries, instead of merely facilitating access to local biological resources. Many in
the developing world are excited with the prospects of genomic medicine. We are at the
crossroads between theory and practice. It is important now that we all think seriously about the
challenges and opportunities lying ahead.
8

8.1 Summary of the Research Findings

In 2007, as part of a larger research project entitled, *Human Genomic Variation implications for global health*, I was given the opportunity to lead two case studies, one in India and the other in South Africa. These case studies would form the backbone of this dissertation thesis. At the time, there were several recommendations for developing countries to invest in infrastructure and capacity in human genomic sciences towards global health; yet very few empirical analyses available describing the experiences of developing countries in meeting this challenge. In an effort to address this gap, our team conducted several case studies of large-scale genotyping initiatives in the developing world. Thus, the primary aim of this dissertation was to provide a qualitative descriptive analysis of the large-scale genotyping projects documenting human genomic variation in India and South Africa. By late 2007, it became clear that the proposed project in South Africa would not proceed; however, instead of cancelling the case study, I went ahead and considered it an opportunity to gain a different perspective. After all, qualitative research can benefit by including an outlier sample. Chapter 4 discussed the results and conclusions of the Indian case study. In addition these findings and conclusions formed part of a peer-reviewed publication, a cross comparison with projects in Mexico, Thailand and HUGO Pan-Asia on which I was lead co-author entitled, *Genomic Medicine and Developing Countries: creating a room of their own*. In the publication, we proposed a ‘roadmap’ for those developing countries looking to invest in human genomic sciences, including, the need for political will and institutional leadership; gaining entrance into the knowledge-based economy; addressing local health needs; and genomic sovereignty. These themes were then explored
further, in the case study in South Africa. In Chapter 5, I discussed the results and conclusions of the case study in South Africa. The results and conclusions of a cross comparative analysis of these case studies featured in Chapter 4 and 5, as well as the additional case studies in Mexico, Pan Asia and Thailand were then used to inform an in depth analysis of genomic sovereignty and inform a discussion in Chapter 7 which focuses on some of the findings and makes recommendations for the way forward.

The case studies featured in this dissertation, as well as the case studies on Mexico, Thailand and the HUGO Pan Asian Consortium, have made a significant contribution to the literature, and since their publication they have generated awareness of large-scale projects in the developing world and influence the creation of a HUGO working group on Genomics and the Developing World. They have been referenced in the scholarly literature[^21][^27][^212][^214][^452][^510] as well as in high-impact policy[^511]. In addition, they have fueled collaborative symposia on emerging regulatory issues on genomic medicine and informed a draft policy agenda on recommendations on how genomics can boost the development of the bio-economy (http://www.oecd.org/dataoecd/45/37/47634101.pdf).

The second part of this dissertation provided an in-depth analysis of the theme genomic sovereignty. Genomic sovereignty emerged as a key element in the case studies in India and Mexico, where it was considered an essential to their ability to initiate locally led large-scale genotyping programs. The analysis has generated a preliminary framework of genomic sovereignty for consideration towards consensus on issues of ownership and access to human genetic materials at both the national and international level.
8.2 Study Limitations

In this dissertation, I have described two qualitative case studies that provide empirical evidence on attempts to initiate large-scale genotyping projects in the developing world. One of the strengths of the study also acts as a significant limitation, the lack of a conceptual framework. When embarking on the research, there was very little empirical evidence on investments in large-scale genomics in the developing world and so these case studies were designed to be maximally exploratory. Qualitative description provides an appropriate framework to achieve this aim, as it does not require that the researcher start with a theoretical framework. At the same time, although interpretive analysis is the objective of qualitative description, there is an overwhelming volume of data, and consequently the results tend to remain surface-level and lack the depth and richness obtained when using a theoretical lens. Thus, although the case studies have been used as part of a larger project to inform policy (oftentimes the main purpose of qualitative description) the findings themselves are limited in their capacity to build theory as the research was not designed to test theory. This also applies to the analysis of genomic sovereignty: the ‘working definition’ is based on a cross-comparative analysis of several case studies; however the findings themselves are preliminary, in that the research was not designed to determine its meaning. Instead, the cross-comparative analysis revealed genomic sovereignty as a theme, which is inductively described but limited in its applicability; regardless as an empirical finding it provides context for a future conceptual analysis of genomic sovereignty. Finally, these case studies provide snapshots of investments in large-scale genotyping projects, within a bounded timeframe; applicability to other situations (generalizability of the findings) may be limited. Still, these case studies were included as part of a larger cross comparison, where they have contributed to developing a preliminary framework that can provide lessons.
8.3 Recommendations for Future Work

The research described in this dissertation, as a result of its design, is preliminary in nature and thus provides numerous opportunities for future research. First, there is an opportunity, given the recent investments in large-scale human genomic sciences, in sub-Saharan Africa, to test the findings of these case studies, specifically, the proposed framework for developing countries interested in pursuing large-scale genomic research. The H3 Africa white paper has referenced this work; namely the opportunities and conclusions featured in chapter 7 of this thesis. Moreover, the H3 Africa project, the Shenzhen Chinese National Biobank and the Southern African Genome Project each provide an excellent occasion to further empirical analyses of investments in large-scale genomic sciences more generally as well as their relationship to health research capacity building in the developing world.

Second, these case studies are early snapshots and follow up research on the subsequent successes and challenges of projects like the IGVC would continue to provide crucial detail on the investment and return in human genome research capacity in the developing world. The IGVC case study highlighted both the lack of regulatory infrastructure and the challenges associated with access and delivery; the need to address these through empirical and theoretical research is critical to achieving public health benefits in India and in the developing world generally.

Third, there is an opportunity to contribute to the public health genomics and public health epidemiology literature and policy by exploring what efforts are being put in place to adapt genetic information being amassed by the projects in India, China, Africa and Mexico to public health. As already pointed out in the limitations, the research described here provides a very early snapshot of these projects, and although the intent was described by key informants to
contribute to local health benefits, there is still little empirical description of the challenges and the opportunities faced by public health genomics model in the developing world. For example, INMEGEN in Mexico has established a nine-point strategy for adopting genomic medicine. Moreover, a related project that has only just been announced by the WHO [see: http://www.who.int/rpc/grand_challenges.pdf - accessed June 12, 2011] aims to develop a “list of the top 10 priorities for the effective development and application of genomics-based interventions for public health improvement in developing countries.

Finally, my analysis of genomic sovereignty has generated a possible framework for consideration towards consensus on issues of ownership and access to human genetic materials at both the national and international level that needs to be further developed and explored through subsequent research. First, where and if human genetic materials are considered sovereign resources, there is a need to determine what is meant by human genetic materials (i.e. is there a difference between the genetic samples, the data and the information). Second, does the working definition of genomic sovereignty hold true, and if so – can it provide a legitimate scope for legislating human genetic materials at the national and international level. The Southern African Genome Project provides an ideal opportunity to explore these questions, given the expressed interest \(^{214, 453}\) by stakeholders in South Africa to establish legislation of this nature.
References


118 Biobanks Act No. 110, Amended No. 88; Amended no. 48 <http://eng.velferdarraduneyti.is/acts-of-Parliament/nr/20093> (Ministry of Welfare, Iceland, 2000, Amended 2008; Amended 2009).


Diamond, Commissioner of Patents and Trademarks v. Chakrabarty 447 U.S. 303 (United States Supreme Court, 1980).


Moore v. Regents of the University of California 51 Cal.3d 120 (Supreme Court of California, 1990).


196 Gorove, S. The concept of "common heritage of mankind": a political, moral or legal innovation? *San Diego L. Rev.* 9, 390-403 (1972).


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Martin, P. & Morrison, M. Realising the potential of genomic medicine. 143 (Institute for the study of Genetics, Biorisks and Society, University of Nottingham, London, UK, 2006).


Rose, H. From hype to mothballs in four years: troubles in the development of large-scale DNA biobanks in Europe. Community Genetics 9, 184-190 (2006).


Kumar, N. K. in Human genetic biobanks in Asia (ed Margaret Sleeboom-Faulkner) Ch. 7, 142-150 (Routledge, 2009).


Yin, R. K. *Case study research: design and methods.* Fourth edn, (Sage Publications Ltd., 2009).

Stake, RE. *The art of case study research.* (Sage Publications, 1995).


Ministry of Health & F.W. Guidelines for exchange of human biological material for biomedical related purposes (Ministry of Health & F.W., Government of India, New Delhi, 1997).


Department of Biotechnology. National Biotechnology Development Strategy (Govt. of India Ministry of Science & Technology 2007).


384 Council of Europe. Recommendation Rec (2006)4 of the Committee of Ministers to member states on research on biological materials of human origin (Council of Europe, Strasbourg, March 15, 2006).


386 Canadian Institutes of Health Research. Policy on Access to Research Outputs 7 (Canadian Institutes of Health Research, 2007).


388 Genome Canada. Data and resource sharing plans 3 (Genome Canada, 2008).


Weiss, T. G. & Hubert, D. in *The responsibility to protect: research, bibliography, background* Ch. 1, 5-14 (International Development Research Centre, 2001).


Burch, K. "Property" and the making of the international system. 175 (Lynne Rienner Publishers, Inc., 1997).


Wallerstein, I. in *States and sovereignty in the global economy* (eds David A. Smith, Dorothy J. Solinger, & Steven C. Topik) Ch. 1, 20-33 (Routledge, 1999).


FAO. International undertaking on plant genetic resources (Food and Agriculture Organization, Rome, Italy, 1983).


Shiva, V. *Biopiracy: the plunder of nature and knowledge*. (South End Press, 1999).


CBD. Bonn guidelines on access to genetic resources and fair and equitable sharing of the benefits arising out of their utilization. 20 (The Secretariat of the Convention on Biological Diversity, Montreal, Quebec, 2002).


Shashikant, S. *Pandemic Preparedness*. (Thrid World Network, 2010).


Battelle Technology Partnership Practice. Economic impact of the Human Genome Project. 1-58 (Battell Memorial Institute, 2011).


Schrijver, N. *Sovereignty over natural resources*. (Cambridge University Press, 1997).


IMF. *World Economic Outlook*. 242 (International Monetary Fund, 2011).

Economist Intelligence Unit. GCC trade and investment flows: the emerging-market surge. 38 (The Economist, 2011).


490 NEPAD. African Innovation Outlook: Executive Summary. 18 (NEPAD, 2010).


Appendix 1

Series of Publications related to the Human Genomic Variation: Implications for Global Health Project

+ Genomic Medicine in Developing Countries Supplement

Available at: http://www.nature.com/nrg/supplements/genomicmedicine/index.html

+ Genomic Medicine and Developing Countries: creating a room of their own

Available at: http://www.nature.com/nrg/journal/v9/n6/abs/nrg2379.html
Appendix 2.


Available at: http://www.nature.com/tpj/journal/v8/n3/full/6500489a.html
Appendix 3.

Indian Genome Variation Consortium

I- BACKGROUND

Please provide a brief overview of the Indian Genome Variation Database genome sequencing project. What are its short and long term objectives?

II- BENEFIT TO DEVELOPING COUNTRIES

In your view, what is the value of genomic variation studies?

What do you see as the limitations of these types of studies?

How might the results of your study be used to improve the health of all the people in India? Globally? What benefits to you foresee for the Indian population? For the global population?

Other than funding, what is the role of the Government of India in the Indian Genome Variation Database Initiative/Consortium.

When you do mutli country SNP consortiums, how do you handle data sharing and intellectual property issues?

How have you worked with regulatory bodies in preparation for this project?

What are the present requirements to approve imported medicines?

Are there examples that you are aware of where a drug is known to work in one population but not in the Indian population?

Are there any requirements to collect genomic information in clinical trials?

What is the legislative and regulatory framework in place (or in planning) that takes into account genomic variation at the population level in clinical trials/drug approval/public health planning?

Do you foresee any bottlenecks in legislative and regulatory frameworks that will impede the adoption of genomic medicine in your country?
Do you have any plans yet on how the results of your studies might be translated into useful health products; are there any plans for commercialization of the knowledge in your country?

Have you considered partnering with any companies (in other developing or developed countries) to derive health products from the acquired knowledge of the Indian Genome Variation Database genome sequencing project?

III-Ethical, Legal, Social Issues (Regulatory Issues)

Describe the research ethics process for obtaining approval for studies of genomic variation in your country

Please describe your approach to consent; obtaining of samples, their storage and the confidentiality issues that may arise. Please describe the process.

Have there been any ethical issues that have arisen in performing this study? Please tell me about them.

What sorts of safeguards do you have in place to ensure minority populations benefit from studies of genomic variation?

How did you go about approaching the communities you wished to sample prior the project?

What are/were their (communities that were sampled) responses to your studies of human genomic variation?

How do you work with the public on matters of genomic variation studies in your country?

Can you provide us with examples of the Indian Genome Variation Database Consortium’s response to any concerns, questions, requests made by the public regarding genomics or pharmacogenomics?

IV-Conglusion

Are there any issues that I have not covered that you consider important to discuss?
Can you suggest any organizations or individuals I should contact who would provide insight into the implications of human genomic variation studies for developing countries?

**University of Cape Town’s (UCT) Division of Human Genetics/The Africa Genome Education Institute (AGEI) (South Africa)**

**BACKGROUND**

Please tell me a little bit about yourself (e.g.: your background, your research/position) [are you involved with human genotyping projects in South Africa – if so how?].

Tell me about your project.

**IF YES - BENEFITS**

In your view, what is the value of your project? What is the value of human genotyping projects which explore genomic variation in developing countries / emerging economies?

In your opinion, are there any limitations to your study? Are there general limitations in developing countries / emerging economies? Can you comment on those?

Can you tell me a little about other genotyping projects (human or otherwise) currently taking place in South Africa? This seems very timely, can you comment on the time in relation to other emerging economies? [highlight India, Thailand, Mexico – also China – large scale genotyping projects]

Do you see South Africa embarking on a single large scale genotyping variation project, somewhat along the lines of those being conducted in India, Mexico and China?

**IF NO - LIMITATIONS**

Why have you not embarked on a genotyping project?

What are the barriers that you have faced?
How can you overcome these barriers?

SOVEREIGNTY

In our previous case studies, we have discovered that genomic sovereignty is a repeating theme.

Are you familiar with the International Convention on Biodiversity? Do you view the human genome as different from flora and fauna? What about the UNESCO statement on the Human Genome, if so what are your thoughts? How would this apply to unique patterns of genomic variation?

Are you aware of any guidelines or legislation regarding the export of human biological samples outside of South Africa? What are your thoughts regarding the export of samples?

How does this – or – would this affect international collaborations?

Are you familiar with any documented evidence of genomic variation in the South African population? Can you describe it to me?

Are you aware of the sovereignty legislation in Iceland as well as that being developed in Mexico? Do you think the same approach applies in South Africa? If not – Why? If so – How?

How might the results of these studies be used to benefit the South African population?

COMMERCIALIZATION

Do you have any plans yet on how the results of your studies might be translated from basic research through to development (e.g.: ancestry and/or lifestyle services, health diagnostics)?

Are there any plans for commercialization of the knowledge? How would you go about achieving this?

Have you considered partnering with any companies (locally or in other developing or developed countries) to derive products (health or otherwise) from the acquired knowledge of your project? How would you describe your ability to access to enterprise/industry? [If poor, how could this access be improved?]
How would you describe the relationship between academia and industry here in South Africa? [If poor, how could this relationship be improved?]

How would you describe the role of the Government of South Africa in human genotyping initiatives? [e.g.: policies / funding, regulation, etc]

What steps should be taken in South Africa (if any) to strategically position itself in the genomics revolution?

Are you involved in any research collaborations, international or otherwise? What are the benefits to participating in these? What are some of the barriers and/or limitations to these?

REGULATORY

How would you describe the regulatory environment in South Africa with respect to human genotyping projects? (e.g.: diagnostics, pharmacogenomics)?

Are there any documented examples of differences between the various South African populations with regards to disease predisposition or drug response?

If so, how might this impact the efficacy of imported medications developed in other populations, mainly located in the West?

Are there any requirements to collect genomic information in clinical trials?

What is the legislative and regulatory framework in place (or in planning) that takes into account genomic variation at the population level in clinical trials/drug approval/public health planning?

Would you favour such an approach if the scientific evidence provided a basis for it?

Do you foresee any bottlenecks in legislative and regulatory frameworks that will impede the adoption of the benefits from these projects (e.g. health and economic benefits) in South Africa?

ETHICAL, LEGAL and SOCIAL ISSUES

Describe the research ethics process for obtaining approval for studies of genomic variation and related studies in your country
Please describe your approach to consent; obtaining of samples, their storage and the confidentiality issues that may arise. Please describe the process. (may have already answered in 19)

Have there been any ethical issues that have arisen in performing this study? Please tell me about them.

What sorts of safeguards do you have in place to ensure minority populations benefit from studies of genomic variation?

How do you work with the communities and the public in getting them to understand what you are trying to achieve and to be able to learn of their wishes?

Can you provide us with examples? [how you may have or would choose to respond to any concerns, questions, or requests made by the public regarding genotyping studies and related technologies]

PRIVATE SECTOR

Will you provide a brief overview of how this company was developed?

Is this company contributing to the development of new genomic technologies in SA? Are these technologies currently being targeted to local health needs?

In your experience, what have been the major barriers to investment in genomics SA?

How has your company attempted to overcome these barriers? Have these actions been successful or ineffective?

What are the incentives to engage in genomics innovation in your country? Has your company taken advantage of these incentives?

Who provides the funding for genomics research and development and commercialization initiatives in your country? Is the funding easily available and sufficient?
Who are the main sources of innovative ideas and necessary expertise in your company?

Please describe if and how your firm is linked with other institutions and firms in the health technology sector. What is the main reason(s) for entering into the partnership? Is the partnership with a public (academic) or private institution? Is the partnership domestic or international? What are the major benefits of the partnership?

Please describe the effects of the regulatory environment in your country on your investment into genomics

Please describe the effects of the intellectual property regime in your country on your investment into genomics (here if time and depending on answer, you can probe on sovereignty issue)

What are your bottom-line needs to invest in genomics for SA?

What incentives, including services and information, would encourage you to invest more in genomics in SA?

Do you collaborate with academic institutions and/or hospitals? How would you describe your relationship with them?

Are genotyping services regulated by the South African MCC? What are the regulations? How are they enforced? Only ask if company is involved in this

Is direct to consumer advertising in the area of genotyping permitted in South Africa? Same as in

CONCLUSION

Are there any issues that I have not covered that you consider important to discuss?

Can you suggest any organizations or individuals I should contact who would provide insight into the implications of human genomic variation studies for developing countries?
Appendix 4.

STUDY INFORMATION AND CONSENT FORM

Research Project Title
Human Genomic Variation: Implications for Global Health

Investigators
Dr. Abdallah S. Daar
Dr. Béatrice Séguin
Dr. Peter Singer
Ms. Billie-Jo Hardy
Dr. Sarah Ali Khan

Funding Agency
Genome Canada

Background and Purpose of Research
This is a research project. The McLaughlin-Rotman Centre for Global Health (MRC), University Health Network (UHN) at the University of Toronto is currently exploring the implications for global health with respect to the emerging trend in applying knowledge of human genomic variation among population groups to understand disease susceptibility and drug response.

Invitation to Participate
You have been invited to participate in a one-on-one face-to-face interview. You will be asked about your views, experiences, with respect to the implications for global health and the emerging trend in applying knowledge of human genomic variation among population groups to understand disease susceptibility and drug response.

Participation
Participation in research is completely voluntary. You are free to choose to participate or not to participate in this research study. If you agree to participate in this study, you may choose to withdraw your participation at any time. You may also refuse to answer any specific questions without any adverse consequences.

Procedures
You have been invited to participate in a one-on-one face-to-face interview that will last approximately 30 minutes to one hour. The interview will be conducted by the investigators (Séguin, Hardy, Daar, Ali Khan and/or Singer) and will be digitally recorded and transcribed.

**When and where will the study take place?**

This is a 4 year study taking place in the US, India, Mexico, Singapore, South Africa, and Thailand.

**Risks and benefits of the study**

The foreseeable risks are the potential that we will disclose what you tell us and attribute it to you. You should not disclose any proprietary information to us. The only benefit is you will help shed new knowledge and understanding of the role of human genomic variation in both developed and developing countries.

**Privacy and Confidentiality**

The one-on-one interviews will be digitally-recorded and transcribed. All digital files and transcripts will be kept on a password-protected computer with access restricted to the research team. All field notes will be stored in a locked cabinet at the MRC-UHN at the University of Toronto. We will assume that we can attribute direct quotations from you unless specified otherwise (see consent form). All raw data (audiodigital files and transcripts) will be stored in a locked cabinet, and only members of the research team at the MRC-UHN at the University of Toronto will have access to them. Confidentiality can only be guaranteed to the extent permitted by law.

**Publication of Research Findings:**

We will publish our results in the appropriate peer-reviewed academic journals, policy briefs, and possible teaching materials. We will present the data at national and international conferences. When we present our results at conferences or in publications, we may identify you by name unless you ask us only to list you among interviewees. Following the completion of our analysis, we may we may contact you to make sure we captured your quotes correctly (referred to as ‘member check”).

**Compensation/Remuneration**

You will not be compensated for your participation.

**Your Rights as a Participant**

You waive no legal rights by participating in this study. If you have any questions about your rights as a research participant, you may telephone the Director of the Research Ethics Review Office at 416-946-3389. You are being given a copy of this information sheet.

I, _____________, agree to participate in a study that

*Name of person*
is examining the implications for global health of the emerging trend to apply knowledge of human genomic variation among population groups to understand disease susceptibility and drug response.

By signing this form, I am indicating that I:

1. Read and understood the Letter of Invitation and the Study Information Form, including the project rationale, description, methodology, research team, and funding, as described therein.

2. Understand that the procedure involves open-ended (face-to-face) interviews with the study investigators and that interviews will be digitally recorded and transcribed.

3. Understand that the information provided during this consultation may be used in academic publications and public presentations.

4. Understand that the only risk in participating in this study is the potential that what I say will be disclosed and attributed to me. I understand that I should not disclose any proprietary information.

5. Understand that I can withdraw from the study at any time without explanation.

6. Have not waived any of the legal rights that I have as a participant in this research study after signing this form.

7. Have been given a copy of this consent form and the study information form.

If you do not wish to have quotations attributed to you, please initial here __________

_________________________________________  ___________________________  ____________
Participant’s Printed Name  Participant’s Signature  Date

_________________________________________
Investigator Name  Date
Appendix 5.

Decree through which the fraction V of article 100 and article 461 is reformed, and articles 317 BIS and 317 BIS 1 are added. All these articles are from the General Health Law.

Felipe De Jesus Calderon Hinojosa, President of the Mexicans United States, to its habitants:

That the honorable Congress has directed me (approached me) with the following

**Decree**

The General Congress of the Mexican United States decrees:

**The fraction V of article 100 and article 461 is reformed, and articles 317 BIS and 317 BIS 1 are added. All these articles are from the General Health Law.**

Single Article: the fraction V of article 100 and article 461 is reformed, and articles 317 BIS and 317 BIS 1 are added. All these articles are from the General Health Law, to be left as follow:

**Article 100.** - The investigation on human beings will be developed conformed to the following:

I. a IV....

V. It (investigation on human beings) can only be performed by health professionals in medical institutions that act under the vigilance of the competent sanitary authorities.

The execution of (population genomic studies ?) should form part of a research project;

VI. VII....

**Article 317 BIS.**- The transference out of national territory of human beings tissues which are referred in article 375 fraction VI of this law that can be source for genetic material (DNA) and whose purpose will be to carry out population genomic studies, is subjected to:

I. To form part of research project approved by the Mexican institution for scientific research conform to the established in article 100 of the law, to the General health Law regulation and to all dispositions applicable, and

II. Obtain the approval referred in article 375 of this law

III. For the effects of this law, population genomic study is understood as that one whose purpose is the analysis of one or more of the genetics markers in individuals no related that describe the genomic structure of a specific
population, identify an ethnic group or identify genes associated to an specific feature, a disease or the reaction to drugs.

The secretary, in coordination with the National Institute for Genomic Medicine as a Federal government advisor and as a national reference centre in this subject, will carry out the registration of the permits mentioned in fraction II of this article.

**Article 317 IBID 1.** - The genetic material referred in the previous article will not be used for different or incompatible purposes to those ones that motivated its acquisition.

**Article 461.** - Those that transfer or attempt to transfer out of the national territory organs, tissues or components from alive human beings or from corpses without approval of the health secretary, will suffer from 4 to 15 years of prison and a bail from 300 to 700 days of minimum salary effective in the economic zone where it happens.

Equal sanction will be applied to those that transfer or attempt to transfer out of the national territory human beings tissues that can be source of genetic material (DNA) destined to population genomic studies contrary to articles 317 IBID y 317 IBID 1 of this law.

If the person responsible (for the illegal transfers) is a professional or technician, or an assistant of any of the health disciplines, the previous sanction will be added to the suspension of her or his professional practice up to seven years.

**Transitory**

Single: the current decree will be effective the next day after its publication in the Official Newspaper of the Federation.

Mexico, D.F., given in the 24th of April, 2008.- **Santiago Creel Mirand**, President.- Depute:. **Ruth Zavaleta Salgado**, presidenta.- Senator. **Adrian Rivera Perez**, Secretary.- Depute **Jacinto Gomez Pasillas**, Secreatary.- (signatures, seals)

In order to comply with what was arranged in the fraction I of article 89 of the political constitution of the Mexican United States, and for its proper publication and observance, I send the current decree in the residence of the federal executive power in the city of Mexico, Federal District on the fourth of July of 2008.-

**Felipe de Jesus Calderon Hinojosa** (signature, seal)

.- Government secretary, Juan Camilo Mourino Terrazo. – (signature, seal)
DECRETO por el que se reforma la fracción V del artículo 100 y el artículo 461, y se adicionan los artículos 317 Bis y 317 Bis 1, todos de la Ley General de Salud.

Al margen un sello con el Escudo Nacional, que dice: Estados Unidos Mexicanos.- Presidencia de la República.

FELIPE DE JESÚS CALDERÓN HINOJOSA, Presidente de los Estados Unidos Mexicanos, a sus habitantes sabed:

Que el Honorable Congreso de la Unión, se ha servido dirigirme el siguiente

DECRETO

"EL CONGRESO GENERAL DE LOS ESTADOS UNIDOS MEXICANOS, DECRETA:

SE REFORMA LA FRACCIÓN V DEL ARTÍCULO 100 Y EL ARTÍCULO 461, Y SE ADICIONAN LOS ARTÍCULOS 317 BIS Y 317 BIS 1, TODOS DE LA LEY GENERAL DE SALUD.

Artículo Único. Se reforma la fracción V del artículo 100 y el artículo 461, y se adicionan los artículos 317 Bis y 317 Bis 1, todos de la Ley General de Salud, para quedar como sigue:

Artículo 100.- La investigación en seres humanos se desarrollará conforme a las siguientes bases:

I. a IV. ...

V. Sólo podrá realizarse por profesionales de la salud en instituciones médicas que actúen bajo la vigilancia de las autoridades sanitarias competentes.

La realización de estudios genómicos poblacionales deberá formar parte de un proyecto de investigación;

VI. y VII. ...

Artículo 317 Bis.- El traslado fuera del territorio nacional de tejidos de seres humanos referidos en el artículo 375 fracción VI de esta Ley que pueda ser fuente de material genético (ácido desoxirribonucleico) y cuyo propósito sea llevar a cabo estudios genómicos poblacionales, estará sujeto a:

I. Formar parte de un proyecto de investigación aprobado por una institución mexicana de investigación científica y conforme a lo establecido en el artículo 100 de la Ley, al Reglamento de la Ley General de Salud en materia de investigación y demás disposiciones aplicables, y

II. Obtener el permiso al que se refiere el artículo 375 de esta Ley.

III. Para efectos de esta Ley, se entiende por estudio genómico poblacional al que tiene como propósito el análisis de uno o más marcadores genéticos en individuos no relacionado que describen la estructura genómica de una población determinada, identifican a un grupo étnico o identifican genes asociados a un rasgo, una enfermedad o la respuesta a fármacos.

La Secretaría, en coordinación con el Instituto Nacional de Medicina Genómica en su carácter de órgano asesor del Gobierno Federal y centro nacional de referencia en la materia, llevará el registro de los permisos que se mencionan en la fracción II de este artículo.

Artículo 317 Bis 1.- El material genético a que se refiere el artículo anterior no podrá ser utilizado para finalidades distintas o incompatibles con aquellos que motivaron su obtención.

Artículo 461.- Al que traslade o realice actos tendientes a trasladar fuera del territorio nacional, órganos, tejidos y sus componentes de seres humanos vivos o de cadáveres, sin permiso de la Secretaría de Salud, se le impondrá prisión de cuatro a quince años y multa por el equivalente de trescientos a setecientos días de salario mínimo general vigente en la zona económica de que se trate.

Igual sanción se aplicará al que traslade o realice actos tendientes a trasladar fuera del territorio nacional tejidos de seres humanos que puedan ser fuente de material genético (ácido desoxirribonucleico) para estudios genómicos poblacionales en contravención de los artículos 317 Bis y 317 Bis 1 de esta Ley.
Si el responsable es un profesional, técnico o auxiliar de las disciplinas para la salud, a la pena anterior se añadirá suspensión en el ejercicio de su profesión u oficio hasta por siete años.

TRANSITORIO

Único. El presente Decreto entrará en vigor al siguiente día al de su publicación en el Diario Oficial de la Federación.


En cumplimiento de lo dispuesto por la fracción I del Artículo 89 de la Constitución Política de los Estados Unidos Mexicanos, y para su debida publicación y observancia, expido el presente Decreto en la Residencia del Poder Ejecutivo Federal, en la Ciudad de México, Distrito Federal, a cuatro de julio de dos mil ocho.- Felipe de Jesús Calderón Hinojosa.- Rúbrica.- El Secretario de Gobernación, Juan Camilo Mouriño Terrazas.- Rúbrica.
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