THE ROLE OF PHARMACOGENOMICS IN CLINICAL RESEARCH IN SOUTH AFRICA: ETHICAL, LEGAL AND SOCIAL CHALLENGES

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DECLARATION

I, Marzelle Haskins declare that this Research Report is my own, unaided work. It is being submitted for the Degree of MScMed (Bioethics and Health Law) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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(Signature of candidate)

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ABSTRACT

Pharmacogenomics (PGx) is a research field where a person's genes are connected to their response to medicine. PGx research can positively influence the way people respond to treatment and treat disease more effectively. PGx research shows promise in clinical trials as better knowledge of the cause for a specific medication response can improve the medicine's safety and therapeutic index. With South Africa's high incidence of communicable and non-communicable diseases, interventions are contingent on prevention and treatment, including drug therapy, leading to toxicity. The South African population exhibits distinctive genetic profiles, and consequently, pharmacogenomics may positively influence the disease burden. With advances in pharmacogenomic research comes social, ethical, and legal challenges and the potential for exploitation. This research report aims to explore these challenges and suggest ethically justified guidelines or criteria that can be incorporated into current health research ethics guidelines when conducting PGx research in clinical trials in South Africa. There are three challenges investigated in this report. The first is the ethical challenges of PGx research. Following this is the legal challenges and, lastly, social challenges. The final chapter consists of suggested ethical guidelines and recommendations when conducting PGx research on human participants in South Africa.

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CHAPTER 1 - INTRODUCTION

Pharmacogenomics (PGx) is a research field where a person's genes are connected to their response to medicine. It has the potential to influence the way people respond to treatment positively. By preventing medicine prescription that may produce serious side effects or have little or no clinical benefit, diseases can be treated more effectively. Genes can affect a patient's response to medicine due to the differentiation in how the body processes the treatment and the variation in diseases' genetic characteristics (Peterson-Iyer, 2008, Karczewski et al., 2012). Due to the high incidence of communicable and non-communicable diseases in South Africa, interventions are contingent on disease prevention and treatment, leading to pharmaceuticals. However, adverse drug reactions to pharmaceuticals are reported in 8.4% of hospitalised patients in South Africa, which sets a substantial financial strain on health care and adds to poor compliance with medication, leading to drug resistance (Moutton et al., 2016).

Research conducted on the South African population's genetic diversity shows that South African people exhibit distinctive genetic profiles that differ from other African populations. Genotyping platforms that capture the pharmacogenomic variety of South Africans can potentially prevent and treat diseases by positively influencing how people respond to medicine (Warnich et al., 2011). Furthermore, PGx research can be promising in clinical trials as better knowledge of the cause for the response to a specific medication can make it possible for scientists to concentrate on the significant aspects of a medicine's action, thereby improving the therapeutic index of the treatment. It can further expedite new medications' development, resulting in smaller, safer, and more cost-effective clinical trials (Peterson-Iyer, 2008). However, with PGx research comes various social, ethical, and legal challenges and the potential for South African research participants and populations' exploitation. Therefore, there is a need to examine the potential ethical, legal, and social concerns that arise from PGx research in South Africa and apply the findings to recommendations for local ethics guidelines in PGx research.

1.1 Background, Literature Analysis and Critique

With the commencement of genetic and Pharmacogenomic health research on human participants, several international publications were published to examine the ethical, legal, and social challenges. For purposes of this report, the following documents were utilised:

- *The Ethical Legal and Social Implications for Pharmacogenomics in Developing Countries* (WHO, 2007).
- *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilisation* (CBD, 2011).
- Nuffield Council on Bioethics: *Pharmacogenetics ethical issues* (Nuffield Council, 2003).
- *Declaration of Bioethics and Human Rights* (UNESCO, 2005).
- *International Declaration on Human Genetic Data* (UNESCO, 2003).
- *International Ethics Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2016).
- *Declaration of Taipei on Ethical Consideration Regarding Health Databases and Biobanks* (WMA, 2016).

The documents mentioned above provides useful guidance on genetic and PGx health research implications from an international perspective. Still, it lacks insight into the unique challenges of PGx research in South Africa. *Ethics in Health Research: Principles, Processes and Structures,* published by the South African Department of Health, does not mention Pharmacogenetic research but allows two paragraphs for genetic and genomic research, not citing the challenges of said research (DOH, 2015). The Academy of Science of South Africa published a Consensus Study, *Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications,* to address genetics and genomics related to research, health service provision, and forensics. However, it does not focus specifically on the wide range of ethical, legal, and social challenges specific to PGx health research (ASSAF, 2018). A need exists for ethics guidelines for pharmacogenomics research in human participants in South Africa that gives guidance on the following:

- informed consent,

- social and cultural differences of research populations,
- the exploitation of research participants,
- benefits sharing,
- access to medicine, and
- confidentiality of the PGx research environment.

1.2 Rationale for the Study

Many international and local declarations, codes, publications, and guidelines, address and discuss ethical issues emerging from advances in biology and medicine (bioethics), including health research in human participants. However, as medical treatment and science evolve, so do the ethical challenges. Pharmacogenomics and the distinctive genetic profiles of South African populations are examples of new scientific concepts that bring unique ethical, legal, and social complications (Warnich et al., 2011). International publications identify and discuss many of these complexities and provide helpful guidance on how to address them. However, these publications lack perception into the exceptional challenges of PGx research in South Africa. Furthermore, there is limited literature on the legal implications of PGx research in South Africa.

The basis of this proposal is to examine international guidance documents on the ethical and social challenges of PGx health research and apply them to local challenges. Incorporating global knowledge into local content will help develop inclusive ethics guidelines for PGx research in South Africa. Furthermore, a review of the potential legal implications of PGx research in South Africa will build a strong foundation towards reviewing existing law to incorporate legal considerations of PGx research.

1.3 Thesis Statement

Pharmacogenetic research can potentially benefit South African populations. Nevertheless, before these benefits can be realised, provision must be made for Ethics Guidelines for Pharmacogenetic research in South Africa to protect the rights of research participants.

1.4 Research Aim and Objectives

This research report explores the ethical, legal, and social challenges of Pharmacogenomic research in South Africa and suggests ethically justified guidelines for conducting PGx research in clinical trials in South Africa.

The research's general objective is to evaluate the above challenges that emanate from Pharmacogenomic health research and recommend ethics guidelines to address the challenges in South African populations.

The research is proposed to:

1. Provide a background on the relevance of Pharmacogenomics research.
2. Identify the ethical, legal, and social challenges related to Pharmacogenomics research.
3. Suggest guidelines on how to address the ethical and social challenges in South Africa.

1.5 Research Methods

I employ a systematic and critical evaluation of current local and international guidelines and publications dealing with the ethical, legal, and social challenges related to PGx health research to identify the shortcomings of local policies and legislation. Once the ethical, legal, and social weaknesses have been identified, I endeavour to use this information to incorporate corrective action in suggested guidelines for conducting PGx research in health research, with specific reference to clinical trials.

The report consists of the following sections:

- The Background of Pharmacogenomics Research
- The Nature of Pharmacogenomics Research in South Africa
- Ethical Considerations Related to Pharmacogenomic Research in South Africa
- Legal Implications of Pharmacogenomics Research in South Africa
- Social Implications of Pharmacogenomics Research in South Africa
- Recommended guidelines to address social and ethical issues of Pharmacogenomic research in South Africa.

CHAPTER 2: BACKGROUND TO PHARMACOGENOMICS AND THE NATURE OF PHARMACOGENOMIC RESEARCH IN SOUTH AFRICA

2.1 Introduction

Before examining the ethical, legal, and social challenges of pharmacogenomics (PGx) research in South Africa, it is necessary to understand the term "pharmacogenomics" and its relevance in research and provide background information on the role of PGx research for South Africa.

The objectives of this chapter are to:
(1) define and explain PGx;
(2) provide background information on the science behind PGx;
(3) illustrate the potential impact of PGx research in South Africa

Specific attention is given to the application of PGx in pharmaceutical research and the influence that PGx research may have on how clinical trials are conducted, and the potential impact of PGx on health research in African populations. Furthermore, objective three is illustrated by looking at the origins of the South African people and the population group's genetic diversities with special consideration to PGx research's relevance in the South African populations and pharmacogenetically relevant genes in these populations.

2.2 Scientific Background

The phrase pharmacogenomics stems from a mixture of pharmacology and genomics (Lister Hill National Centre for Biomedical Communications, 2020). Pharmacology is the study of how medicine functions in the body, whereas genetics explains the variance and similarities between inherited characteristics or organisms (Center for Genetics Education, 2015). Thus, the interface between medicines and genetics has been labelled pharmacogenomics (PGx). It can be defined as studying the relevance of genetic factors on the body's response to medicines or pharmacology. PGx is not limited to changes in genes but also looks at how medicines influence how genes work (Peterson-Iyer, 2008; Karczewski et al., 2012). Genetic variations in paths involved in medicine absorption, distribution, metabolism, and excretion (ADME) signify the leading objectives of PGx studies (Tshabalala

et.al., 2019). For medicine to fulfil its anticipated pharmacological action, complex events such as absorption, transportation, and metabolism need to occur. For these events to occur, specialised proteins are necessary, and the genes that program the proteins can influence individual variations in medicine response. PGx relies on the capacity to identify and characterise genomic differences that impact response to medicine (WHO, 2007). Pharmacogenomic discovery and clinical application require the capability to measure genotypes or the genetic codes in cells correctly. Combining this genetic data and linking it with a phenotype is where genomic information becomes significant. A phenotype can be defined as an observable physical or biochemical characteristic or trait of an organism. Phenotypes may influence the body's ability to metabolise medicines, resulting in poor metabolisers, intermediate metabolisers, extensive metabolisers, and ultra-rapid metabolisers. If medication is metabolised too quickly (ultra-rapid or extensive metabolisers) it may not effectively treat a specific disease or condition. When patients have reduced enzyme function, they cannot fully convert medicines which lead to intermediate metabolisers. If the medicine is broken down too slowly (poor metaboliser), there is a possibility of the build-up of toxic medicine levels in the body, which may cause serious adverse effects (Johnson & Radford, 2016).

Poor and extensive metabolisers can be demonstrated by using the example of the hepatic CYP2D6 enzyme. CYP2D6 is an enzyme in the liver accountable for the breakdown of roughly 25 – 30% of prescribed medicines. A person's ability to metabolise medication into active metabolites is known to differ substantially due to genetic polymorphism resulting in phenotypical inconsistency of the CYP2D6 enzyme. Variations in the CYP2D6 gene were shown to change the activity of the CYP2D6 enzyme and either result in certain medicines not being effective or causing toxicity-related severe adverse events (Nuffield Council on Bioethics, 2003; Johnson & Radford, 2016)). An example of a medicine that requires CYP2D6 to be broken down and removed from the body is the pain killer codeine. CYP2D6 transforms codeine into its active metabolite, morphine, which is responsible for the pain-relieving effect. People who carry two inactive copies of CYP2D6 may not get sufficient pain relief from codeine because of the reduced morphine levels and are considered poor metabolisers. People who carry more than two active copies of CYP2D6, namely ultrarapid metabolisers, metabolise codeine to morphine faster and

may experience symptoms of morphine overdose with a normal dose of codeine (Dean, 2017).

Similarly, differences in response to antiplatelet therapy, clopidogrel, are considered highly heritable and can be explained in part by the CYP2C1 enzyme responsible for the medication's hepatic bioactivation. An estimated one-fourth of patients given clopidogrel display a subtherapeutic response and inconsistent platelet reactivity associated with various risk factors. Patients who are considered poor metabolisers are observed to have a bigger risk of ischemic events, whereas high metabolisers have an increased risk of bleeding (Brown & Pereira, 2018).

From the above examples, it is evident that studying the significance of genetic influences on the body's reaction to medicines can potentially present substantial benefit in advancing medicine use. It will successfully treat disease and prevent medication prescribing to patients who are unlikely to respond or who may suffer severe adverse reactions. PGx may, therefore, make safer and more cost-effective utilisation of pharmaceuticals a reality (WHO, 2007).

2.3 Application of Pharmacogenomics in Clinical Trials

The South African National Health Act (No 61 of 2003) does not explicitly define clinical trials, but it defines health research as follows: "any research which contributes to knowledge of-

(a) the biological, clinical, psychological, or social processes in human beings.
(b) improved methods for the provision of health services.
(c) human pathology.
(d) causes of disease.
(e) the effects of the environment on the human body.
(f) the development of new application of pharmaceuticals, medicines and
(g) the development of new applications of health technology."

The *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa* defines clinical trials as: "Any investigation in human participants (including patients and other volunteers) intended to discover or

verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining their safety and/or efficacy" (DOH, 2006).

It is expected that pharmacogenomics will substantially change how clinical trials are conducted. Typical clinical trials research consists of pre-clinical trials, clinical trials (phase 0 – III), and post-marketing trials (phase IV), which can potentially amount to billions of dollars in research costs (WHO, 2007).

Pre-clinical or laboratory studies include cell studies and animal studies, and once these studies are completed and show clinical promise, the investigational new treatment can be tested in people (American Cancer Society, 2020).

Phase 0 clinical trials help streamline and accelerate the treatment approval procedure by testing a few small treatment dosages in a small number of people to determine how the treatment performs in the body and how participants react to it. The treatment is usually given for a short period, and this phase is not a compulsory phase of clinical trials (American Cancer Society, 2020).

Phase one clinical trials are often called exploratory research and are the primary trials on a novel compound or new formulations in humans, with the primary objective to assess the safety and toxicity of the medicine in human participants. Phase I trials are usually conducted on no more than 100 human participants who are typically healthy. Researchers explore the pharmacokinetics (PK) and pharmacodynamics (PD) of medicine. PK determines how the treatment is absorbed, metabolised, and eliminated from the body, whereas PD determines side effects (PhRMA, 2015; American Cancer Society, 2020).

Phase II trials require a more significant number of participants (100 – 500) with the disease or condition under research. The research is not aimed at providing the conclusive safety and efficacy data required for the approval and registration of new medicine and may include PK and PD. Researchers also investigate the optimal

dose strength and schedules for using the medication and assess possible short-term adverse effects and risks. Phase 2 trials can be split into Phase 2a and Phase 2b. Phase 2a focuses on dosing requirements to find an association between the dose of medicine and the response to the medicine. Phase 2b is designed to determine efficacy in treating, preventing, and diagnosing disease (PhRMA, 2015; American Cancer Society, 2020).

Phase III trials are usually conducted on 1000 to 40,000 participants world-wide and are a source of necessary statistical data regarding the safety, efficacy, and general benefit-risk ratio of the investigational medicine. It usually compares a new medication to the standard of care treatment or placebo. This phase of research is the most expensive and time-consuming and is used to obtain approval and registration of the new medicine from regulatory authorities (PhRMA, 2015; American Cancer Society, 2020)

Phase IV trials are carried out subsequent to the marketing or registration of the pharmaceutical compound and are performed based on the product traits on which marketing authorisation was awarded. It usually takes the form of post-marketing observation, measurement of therapeutic significance, and treatment approaches. The treatment is assessed in thousands of patients to allow for better investigation on short- and long-lasting adverse events and safety (DOH, 2006; National American Cancer Society, 2020.).

In phase I clinical trials, PGx can be utilised by obtaining DNA samples from participants and comparing this with the investigational medicine response profiles. A variable response can be analysed, and if the cause of the variation indicates a connection with a genetic profile, it can potentially affect the inclusion of participants in phase II. In phase II trials, genetic data can be used to guide dosing relevant to various genotypes and thereby potentially exclude participants who may not respond or could suffer unacceptable side effects. In both phase I and II clinical trials, a PGx test can be implemented to stratify research participants based on their genotypes that correlate to their metabolising capability to prevent adverse drug reactions (Dandara et al., 2011). In phase III clinical trials, pharmacogenomics may limit trial participants according to genetic profiles/response to medication, resulting in poor

responders or adverse responders being excluded, resulting in smaller and more specialised trials. (WHO, 2007).

The introduction of PGx during pharmaceuticals development can inform the development process and enhance medications' effectiveness and safety. This may substantially reduce development costs and can be employed at several steps along the medicine discovery pipeline to expedite a simplified, safer, and cost-effective clinical trial process. Ideally, only participants with a genetic profile appropriate for the investigational product in question will be included in phase III trials (Peterson-Iyer, 2008). Suppose information about PGx can be discovered from genomic investigations early in the development cycle. In that case, it could result in smaller clinical trials and the development of medicines explicitly suited for those who are most likely to benefit (Warnich et al., 2011).

PGx research can add the following potential value to the clinical trial process:

- Provide evidence of pharmacogenomic interaction with the medication or evidence that genetic variation is not clinically relevant;
- Detect populations that would benefit by receiving higher or lower doses of medication;
- Help determine if selection criteria for dose-finding studies should be amended to include or exclude a particular group of patients;
- Identify critical stratification and enhancement factors for all phases of clinical trials;
- Assist in advancing informative labelling for therapeutic products under review for regulatory approval (US Department of Health and Human Sciences, 2013).

There are also some limitations to the use of PGx in clinical trials:

- One test cannot fulfil the purpose of all. Several genes will likely be involved in the way a participant reacts to a specific medicine;
- Identifying the genetic differences that may influence medication metabolism or response will be time-consuming, complicated, and expensive;

- Interactions with other medications and environmental factors will have to be established before conclusions can be made about genetic influence and
- It is challenging to induce PGx into health-care settings (Centre for Genetics Education, 2015).

2.4 Pharmacogenomics Research in Africa

The earliest reported humans are thought to originate from Africa, which makes this continent renowned for its extensive genetic diversity (WHO, 2007). The addition of PGx research in pharmaceutical research conducted in Africa can improve health by providing scientific and technical knowledge that may bring down costs and reduce medicine's side effects. The African continent is not merely a large market for new medications and therapies but also an essential human genetic variation depository. Still, African researchers and populations are severely under-represented in current efforts to build capacity that can connect genetic differences to the tendency to get certain diseases and the ability to predict, diagnose, monitor, and treat diseases. This has resulted in limited scientific and economic development in this area (H3A Working Group, 2011).

Successful treatment for complex diseases based on genetic contributions has been applied worldwide, yet, compared with the rest of the world, uptake in Africa has been less. This is due to a lack of capacity, clinical appropriateness, and lack of understanding of disease and treatment's genetic influence. Even though Africa carries an unevenly large burden of infections and non-communicable diseases, most of the genomic research studies have been done in European ancestry populations (Tshabalala et al., 2019). More than 300 medicines contain FDA pharmacogenetic product information, and 100 medicines contain FDA pharmacogenetics guidelines. Yet, only 15 of these medicines have been studied in Africa due to many diseases either being restricted to Africa (e.g. schistosomiasis and malaria) or excessively influencing African populations (e.g. HIV/AIDS, meningitis, tuberculosis) (Radouni et al., 2020). One of the biggest killers in Africa is Malaria, with 81.7% of registered malaria cases. Still, during a recent review of clinical PGx studies in African populations, a single study on malaria treatment was

found. However, due to the high prevalence of HIV and TB in Africa and the focus on variations known to influence anti-retroviral efficacy and outcome, the focus on PGx in TB and HIV has increased in recent years (Radouni et al., 2020). In the past, infectious diseases such as malaria, TB, and HIV were the main reasons for morbidity and mortality in Africa. In contrast, non-communicable diseases such as cardiovascular disease and cancer were attributed to developed countries. However, due to lifestyle changes in many African countries, an 'epidemiological transition' has occurred, where these countries currently carry the weight of infectious and non-infectious diseases (Dandara, 2019).

In March 2009, the Human Hereditary and Health in Africa (H3Africa) Initiative came about from a partnership between the African Society of Human Genetics (ASHG), the Wellcome Trust (WT) (United Kingdom), and the National Institutes of Health (NIH) (United States). The H3Africa initiative aims to increase novel research into the genetic and environmental origin for human diseases of importance to Africans and capacity building for genomics research on the continent. H3Africa aspires to speed up genomics research related to genetic differences in humans that will be relevant to and advance African populations and societies. It aims to achieve this by encouraging infrastructure improvement, training, and distinctive research projects. One of the concerns expressed by H3Africa is high morbidity and mortality rates in communities that are critically afflicted by disease and have poor access to resources. PGx research can be applied to many conditions that afflict the African continent, and the added potential to influence the treatment of non-communicable diseases such as cancer is immense. In 2018 it was reported that the H3A consortium is jointly handling samples and data for over 70,000 participants throughout the continent, including valuable clinical information on various non-communicable and infectious diseases. The consortium has also invested in creating biorepositories and training programs for researchers and health-care professionals (Mulder et al., 2018).

The African Pharmacogenomics Consortium (PAC) was launched on 6 September 2018. The PACs objectives are to encourage PGx research and its clinical application for the safe and effective use of medicines in Africa. The PAC aims to reach these objectives by measuring disease burden, comprehending the underlying

biochemical methods, assessing the health-care system's costs, and discovering interventions for enhanced outcomes. They will do this by using a responsible innovation approach. The PAC vision is to investigate the diverse African genome to understand essential pharmacogenetics and better African patients' quality of life. The main objectives of the PAC are:

- To create awareness of PGx among Africans;
- Research and training in PGx in Africa;
- Implementation of PGx in Africa (Dandara, 2019).

Another area that should be considered when studying PGx in African populations is the widespread use of herbal medicinal plants in addition to pharmaceutical medicines, as this may influence the efficacy and toxicity profiles of pharmaceuticals. For example, the herbal medicinal plant *Moringa oleifera* has inhibitory properties targeted at the cytochrome P45 enzymes and affects the proportion of medication delivered to the site of action in some HIV/AIDS and TB medicines (Matimba et al., 2016).

Primary health care for many African populations include herbal and traditional medicine and is considered generally safe by these populations. Factors that enable frequent usage of herbal and traditional medicines are local availability, lower costs, cultural significance and history of efficacy. With reference to pharmacogenomics, herbal remedies are metabolised by drug metabolising enzymes (DMEs) which has various consequences for therapeutic efficacy. It is therefore essential to consider the pharmacogenetics effects of DMEs when herbal medicines are used as a source of therapy. Yet, the pharmacogenomic implications of the use of herbal and traditional remedies have not been adequately investigated. Although both traditional and conventional remedies can be used effectively, access to conventional treatment in many African populations are limited. It is therefore essential to include knowledge skills and benefits of traditional medicine into modern health care systems. This can be achieved by establishment of appropriate guidelines for monitoring and use and side effects for traditional medicines, which will improve the worth and cautions use of traditional medication (Thomford et al., 2015).

Several low- and middle-income countries have started identifying and differentiating the genetic variations within their populations with the prospect to improve future health. Identifying these genetic variations presents a big market for developing new medicines and is also repositories for imperative human genetic variation to define population subgroups better. This information may identify side effects and benefits from a particular medication not seen in mainly Caucasian populations. Also, PGx research can further benefit African people in the following way:

- Shelved medicines could be licensed and developed in African populations that are not genetically predisposed to adverse drug reactions.
- Developing new medicines using PGx will be more cost-effective. It will result in cheaper medication in developing countries as medicines are created exclusively for populations liable to benefit and experience fewer side effects.
- Compounds discovered during research in African populations that apply to specific minority subpopulations may be of value to the pharmaceutical industry in developed countries, i.e. financial benefit (WHO, 2007).

Even though research interest in PGx is still underrepresented in Africa, it offers opportunities to discover knowledge directed at decision-making methods to update vital medicines lists in African. Furthermore, it can affect personalised medicine decision-making on medications likely to have the most advantage in advancing African populations' health (Mulder et al., 2018).

2.5 Genetic Diversity and Pharmacogenomics in South Africa

Nobel Peace Prize winner, Archbishop Emeritus Desmond Tutu, branded South Africa as The Rainbow Nation due to its extensive assortment of cultures and populations (Warnich et al., 2011). The South African population is divided into four different categories, namely African (79.2%), White (8.9%), Coloured (8.9%), and Indian/Asian (2.5%) (Anon., 2017). Africa is considered the source of the first reported humans, and as a result, African populations are known for their significant genetic variety. Southern African people have demonstrated the greatest degree of

genetic variation and the most within-population variety. South Africans of African origin have reportedly stemmed from two key groups: the Khoisan and the Bantu (Warnich et al., 2011). The first modern-day humans in Southern Africa were the Khoisan speakers, who arrived approximately 20 000 years ago. The Khoisan, also known as San or Bushmen, are indigenous hunter-gatherer societies from various Kalahari Desert regions in Southern Africa. They are the oldest known ancestry of the modern human. Research has shown that two Southern African Khoisan individuals who live a short distance from each other have more genetic diversity than Asian and European individuals living on separate continents (Schuster et al., 2010).

Agricultural Bantu-speakers migrated from West Africa throughout sub-Saharan Africa and arrived in Southern Africa approximately 4,000 years ago (Sirugo et al., 2008). Even though there is an above-average occurrence of within-group genetic differences in the Bantu people, there is a degree of similarity between the groups, which indicates a standard familial population. The Khoisan and Bantu can be clearly distinguished from each other, but a certain amount of admixture has occurred between these groups over time (Warnich et al., 2011).

A few thousand years after the Bantu speakers' arrival, European immigrants (mostly Dutch, French, and British) arrived in South Africa. These immigrants were accompanied by slaves, political convicts, workers, and traders who mainly stemmed from East Africa, Asia, and India. The Caucasian and Indian South Africans are genetically similar as most of their lineage have been recognised as coming from European or Indian ancestors. Still, both populations display small quantities of Africans' gene flow (Warnich et al., 2011).

The South African Coloured or Mixed Ancestry populations display the highest admixture intensity globally and originated approximately 350 years ago. This population admixture transpired due to enslavement by European settlers in the Cape and ethnic influences on the Cape slaves made from East Africa, Madagascar, India, and Indonesia. In addition to the settler-slave ties, unions with the local Khoisan were commonplace (Patterson et al., 2010). Genetic research looking at the genome-wide distinction of the South African Coloureds shows descendent

contributions from at least four diverse origins, namely Xhosa, Khoisan, European and Asian. The greatest generates from the Khoisan (Warnich et al., 2011).

The above-mentioned heterogeneous history of South African populations has resulted in a wide range of genetically diverse populations, a valuable tool to clarify genetic contributors to complex disorders and response to medication (Warnich et al., 2011).

2.6 The Relevance of Pharmacogenomics in South African Populations

The high population admixture found in South Africa affects genome heterozygosity (a measure of genetic variation to the specific location or position of a gene), consequently influencing the phenotypes related to health. Genetic admixture can greatly influence medical and pharmaceutical research. It is an essential tool for comprehending population genetic variation models to comprehend genetic diversity's influence on human disease progression (Patterson et al., 2010).

Approximately 1% of the South African population develop active tuberculosis (TB) each year. Statistics show that about 80% of South Africans are infected with TB bacteria, the majority having latent TB. In 2018 a total of 63,000 people died of TB, of which roughly 42,000 were also HIV positive (Kanabus, 2020). South Africa's per-person health load is the greatest of any middle-income country globally. The South African population is confronted with high incidences of both communicable and non-communicable diseases. (Warnich et al., 2011). Some of the most common non-communicable conditions are cardiovascular disease, diabetes mellitus, and cancer, increasing daily due to an escalation of risk factors such as demographics and socioeconomic inequalities. Solutions aimed at dealing with the high disease burden depend a great deal on prevention and treatment, which necessitates the use of medicines, leading to toxicity or adverse drug reactions (ADRs) (Warnich et al., 2011).

Information on the burden of serious adverse drug reactions (ADRs) in Southern Africa is limited due to colliding epidemics of infections and non-communicable disease, pharmacogenetic variants, simultaneous use of traditional medicines, and an overloaded healthcare system. In an observational study conducted in four

hospitals in three provinces in South Africa, it was found that 8.4% of admissions to adult medical wards were a direct result of ADRs. Medication used in the management of TB and HIV was associated with one-third of these admissions. Approximately half of the admissions were found to be preventable (Moutton et al., 2016). Identifying patterns of existing genetic variations in South Africa will play a significant role in optimising the benefit-risk ratio of medication. It may help comprehend the disparity in the effectiveness and toxicity of therapies to treat communicable and non-communicable diseases and may prove vital to improving South Africans' health (Sirugo et al., 2008; Mpye et al., 2017).

2.7 Pharmacogenetically Relevant Genes in South African Populations

Although Southern African individuals have demonstrated the highest genetic diversity level, implementing pharmacogenomics has been relatively slow. South Africa is gradually building resources supporting progressive genomic technologies, but pharmacogenomics research in Southern Africa is still trailing behind the USA, Europe, and Asia (Mpye et al., 2017). Most of the PGx research in Southern Africa is focused on the Cytochrome P450 (CYP) enzymes. The CYP family of enzymes plays a vital role in medicine metabolism, and approximately 80% of frequently use medicines are substances that act on enzymes encoded by genes in this family (Dandara et al., 2011). Therefore, genetic differences in the way genes are coded for CYP enzymes may explain some of the above noted adverse drug reactions and may be particularly relevant in the South African public health context.

CYP2B6 is necessary to metabolise efavirenz (EFV) and nevirapine, two of the treatments used as first-line antiretrovirals for HIV/AIDS in South Africa. The incidence of CYP2B6 variants is spread unevenly globally, with African populations reporting >40% variants. Genetic variants of CYP2B6 have been associated with EFV plasma concentrations and are associated with Central Nervous System (CNS)-related side effects and neuropsychological toxicity. Therefore, compared to other world populations, African and South African populations are more likely to present with CNS-related adverse effects when taking EFV (Mpye et al., 2017). Another example relates to the CYP2C19 enzyme, responsible for metabolising medicines used in the treatment of malaria, HIV/AIDS, depression, and thromboembolic diseases. Genetic variants on this enzyme are associated with ADRs and treatment

failures. Specifically, individuals carrying the CYP2C19*2 allele (one of two or more alternative forms of a gene, only one of which can be present on a chromosome) are more likely to have a gene-medicine interaction with a medicine called clopidogrel and is more likely to be subjected to cardiovascular events or death (Warnich et al., 2011).

In 2013, a study on the genetic variations in the CYP3A4 enzyme in three South African populations was conducted. The research aimed to detect the genetic variation within the CYP3A4 enzyme in 29 Khoisan, 65 Xhosa, and 65 Mixed Ancestry (MA) individuals. The CYP3A4 enzyme metabolises 50 – 60% of all prescribed medicine and is frequently involved in unfavourable medication interactions. The above research identified 24 variants in the CYP3A4 gene in the three specified population groups, and two uncovered new alleles. The discovery of these new alleles substantiated the concept that novel alleles may have a practical significance in PGx and highlight that new variations to the human variome (the whole set of genetic variations found in populations) still exist. It stresses the need for re-sequencing studies, specifically in the under-represented African people. Furthermore, when assessing the meaningful differentiation in the allele incidences between the Khoisan, Xhosa, and Mixed ancestry, it was noted that the three groups varied substantially from one another, which reflects the distinctive genomic constitution of South Africans. The above research provides a good example of how PGx treatments may vary between population groups, reminding us that medicines intended to treat one population, may be detrimental to another population group (Drögemöller et al., 2013).

During 2018 - 2019, a study was conducted in Soweto, South Africa, including 40 unrelated Black South African persons of Bantu Ancestry. The research used directed next-generation classification to meticulously screen the exons (coding sections of an RNA transcript, or the DNA encoding it, that are translated into protein) of 65 genes responsible for metabolism and therapeutic outcome of most of the medications currently used. It was the first study to methodically evaluate the pharmacological relevant genes in individuals of Bantu descent. The variant composition of 65 pharmacologically essential genes was mapped, leading to the classification of 1662 variations of high confidence, of which 129 were new

(Tshabalala et al., 2019). Evaluation of gene variations was founded firstly on their significance to medication frequently prescribed in the populace representing the research cohort, with specific reference to HIV and TB. Apparent differences were noted between African people and those of European or Asian heritage. Many of these differences are known to substantially influence medicine therapy which may account for the variance in populations' reaction to the same treatment. The above research confirms the existence of great pharmacogenomic diversity in South Africa. It emphasises the need for future research to develop and improve tailored pharmaceutical intervention strategies (Tshabalala et al., 2019). South African populations' distinctive genetic profiles bring rare challenges and exceptional opportunities for advancing and applying pharmacogenomics testing and new gene-specific treatment in South Africa. Although some South African populations will have to be studied independently, more general genetic diversity studies will also have to be conducted to determine to what degree different African populations differ from each other (Warnich et al., 2011).

2.8 The Way Forward

The preceding paragraphs highlight the extensive genetic diversity in African and South African populations, which offers opportunities for discovering and clarifying new therapeutic alternatives of clinical importance. However, more knowledge is needed before these opportunities can be translated into the benefits of precision medicine that can play a role in diagnosing, preventing, and treating the communicable and non-communicable diseases responsible for the disease burden in South Africa. Although insight is gained from the research conducted by Tshabalala and others, more detailed comprehension of population-specific variants is necessary to drive the advancement of pharmacogenomic-based discoveries for precision medicine in patients of African heritage (Tshabalala et al., 2019).

2.9 Conclusion

The study of the significance of genetic influences on the body's reaction to medicine can potentially advance medication use by preventing the prescription of treatment to patients unlikely to respond or suffer serious side effects. It may result in more cost-effective use of medicines as PGx selection of participants in clinical trials may result in smaller, more specialised clinical trials. In line with Africa's genetic diversity, the

addition of PGx research in pharmaceutical research can improve health, bring down costs of treatment and reduce side effects. Thus far, Africa and Southern Africa have made a relatively small contribution to PGx research worldwide. Still, partnerships such as H3Africa and PAC have gone a long way towards developing genomics research in Africa.

Nevertheless, more scientific ventures to study genetics and health in Africa are needed to comprehend the disparity in the effectiveness and toxicity of therapies to treat diseases. The research conducted by Drögenmöller in 2013 and Tshabalala in 2018-2019 shows substantial variations in genomic compositions in the South African populations, which is a clear indication that medicines used to treat one group of South Africans may not benefit another. These results provide us with an excellent justification to apply PGx research in South African populations to address the disease burden.

CHAPTER 3: ETHICAL CONSIDERATIONS RELATED TO PHARMACOGENOMIC RESEARCH IN SOUTH AFRICA

3.1 Introduction

This chapter aims to explore the concept of health as a fundamental human right as it relates to health research and, specifically, health research in Pharmacogenomics (PGx). Furthermore, it aspires to identify the relevant ethical principles when conducting health research and then applying them to Pharmacogenomic (PGx) research in South Africa. A broad overview of the basic principles of beneficence and non-maleficence, distributive justice, and respect for persons is provided. Specific attention is given to the concepts of access and benefit-sharing related to the principles of distributive justice and consent and confidentiality as it relates to the principle of respect for persons.

3.2 Health as a Right

Thoughts around social equality and non-discrimination surfaced throughout the 19th and 20th centuries. Still, only after the second world war, as a consequence of the Nazi atrocities in concentration camps, did human rights got official recognition (Moodley, 2017). This was as a result of the adoption of the *Universal Declaration of Human Rights* (UDRH) by the United Nations General Assembly on December 10, 1948, and the *Constitution of the World Health Organisation* on April 7, 1946.

The UDRH includes health as a fundamental human right for everyone, and article 25 states explicitly that "everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing, and medical care" (UN.,1948). Many of the rights protected in the UDHR have consequently been replicated in other human rights documents and agreements that the Member States has endorsed. A considerable amount of the UDHR is now codified into mandatory human rights obligations worldwide. The World Health Organisation (WHO) emerged from the International Health Conference in 1946, and its Constitution was signed on July 22, 1946, and enacted on April 7, 1946. The objectives of the WHO is the realisation of the highest possible level of health by all peoples. The state parties to the WHO declares the following in its Constitution: "Health is a state of complete physical, mental and social well-being,

and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, political belief, economic, or social condition." The most recent Constitution review was adopted on September 15, 2005 (WHO, 2005). After adopting the documents mentioned above, several human rights conventions were adopted worldwide, which placed direct obligations on governments to meet their people's human rights. However, under the apartheid laws in South Africa, numerous human rights, including the right to health and medical care, were disregarded. The majority of South Africans were reduced to mere physical objects. The right to health became dehumanised as the emphasis was placed on diseases rather than patients, families, and communities (Moodley, 2017). After the fall of apartheid, *The Constitution of the Republic of South Africa* (Act 108 of 1996) (the Constitution) was drawn up by the Parliament elected in 1994 in the South African general election. It was promulgated by President Nelson Mandela on December 18, 1996 and came into effect on February 4, 1997. As indicated in the preamble, the objective of the Constitution is to "heal the divisions of the past and establish a society based on democratic values, social justice, and fundamental human rights". Chapter two of the Constitution mandates a Bill of Rights that outlines human rights that apply to each person, and section 72(1)(a) specifically states that everyone has the right to have access to healthcare services.

3.3 Health Research and Health Research Ethics in South Africa

The South African Constitution (Act 108 of 1996) recognises health as a human right and protects against health research abuse. In section 12(2) the Constitution stipulates that "everyone has the right to bodily and psychological integrity, which includes the right not to be subjected to medical or scientific experiments without their informed consent". Of note, this is a non-derogable right and hence cannot be subjected to limitations. Further prominence is given to health research and health research ethics in the National Health Act of the Republic of South Africa (NHA) (Act 61 of 2003). The NHA stipulates "that research or experimentation on a living person may only be conducted with the written consent of the person after he or she has been informed of the nature of the research or experimentation and any possible positive or adverse consequences on his or her health" (s 71(1)). In section 72(1), the NHA establishes the National Health Research Ethics Council (NHREC) to

advise the Minister of Health on policy and legislation on research ethics and requires that all research or experimentation on humans and animals have to be approved by a health research ethics committee (HREC) (s73).

To guarantee that South African populations are treated justly and with respect by health researchers and that health research stands up to ethical scrutiny, the NHREC produced a guidance document titled, "*Ethics in Health Research: Principles Processes and Structures", (*hereinafter referred to as *South African Ethics Guidelines)* which was updated in 2015 (DOH, 2015). These guidelines have drawn on the NHA as well as the most prominent international ethics guidelines such as the *Declaration of Helsinki* (WMA, 2013), the *Belmont Report* (National Commission for the Protection of Human Subjects, 1979), the *International Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2016) and the *Universal Declaration on Bioethics and Human Rights* (UNESCO, 2005).

In addition to the above, the Health Professionals Council of South Africa (HPCSA) published a comprehensive series of *Guidelines for Good Practice in the Health Care Professions* booklets. Booklet 13 deals specifically with *General Ethical Guidelines of Health Research,* and Booklet 14 deals with *General Ethical Guidelines for Biotechnology Research*. These guidelines have regulatory status because they respond to the Health Professions Act (Act 56 of 1974) and are in harmony with the law (HPCSA, 2016).

Both the South African Ethics Guidelines and the HPCSA Guidelines identify the main ethical principles considered when conducting health research in human participants in South Africa. They are beneficence, non-maleficence, justice (equity), and respect for persons (dignity and autonomy) (DOH, 2015; HPCSA,2016). These principles, derived from the common morality theory, originating from the four principles recommended by Beauchamp and Childress in *Principles of Biomedical Ethics* and are significant for grasping the modern approach to ethics in healthcare (Beauchamp & Childress, 2009). Common morality stems from norms of right and wrong in human behaviour that developed into a long-standing social contract of common morality. It can be perceived as a social agreement with basic standards shared by all and constitutes norms that can be applied universally and include

criteria for behaviour and honourable character qualities such as truthfulness and kindness. It also substantiates human rights (Dhai, 2017).

The principles mentioned above represent a broad framework for dealing with ethical challenges in biomedical research. However, they are not exhaustive and may not always be the most suitable for resolving the specific ethical challenges related to PGx research. For each challenge, the principles will have to be explored objectively with reference to relevant literature to arrive at the most appropriate implementation manner related to PGx research (WHO, 2007).

3.4 Applying Ethics Principles in Pharmacogenomics Research

3.4.1 Beneficence

Beneficence suggests acts or traits that include kindness, compassion, generosity, humanity, goodwill, and sympathy, and it is reminiscent of altruism (unselfish regard for the welfare of others). The idea of beneficence is comprehensive, and from an ethical viewpoint, it includes all norms and conduct to promote the good of other persons. Beneficence, therefore, places a moral duty to act for the good of others, usually by avoiding or eliminating harm, and it puts a responsibility on us to play a role in the positive welfare of persons. It requires constructive steps to help others and not merely the avoidance of harmful acts. However, beneficent actions may also be from non-obligatory, voluntary moral ideals since general morality should not require beneficent acts to include relentless self-sacrifice for others' good. (Beauchamp, 2019).

The question that arises is: When is a beneficent act obligatory, and when is it a moral ideal? Some philosophers (e.g. Peter Singer) believe that beneficence obligations require relentless sacrifice and excessive generosity, whereas others (e.g. Bernard Gert) accept no moral rules of beneficence, only moral ideals, and therefore no general obligation of beneficence (Beauchamp, 2019; Gert, 2017; Singer, 1972). Nevertheless, common moral philosophy requires both not harming and helping to be obligatory and offers some rules of beneficence that we are compelled to follow objectively. We must make efforts to assist others under conditions of minimal risk to ourselves (Beauchamp, 2019).

Applying the principle of beneficence to biomedical research is traditionally recognised as an abstract norm such as "Do no harm" and "Balance benefits against risks". Beneficence is achieved by deliberately avoiding doing harm and determining that risks are in acceptable proportion to potential benefits. Benefit-risk assessments and different ways of acquiring benefits are therefore essential in health research and should be considered by Health Research Ethics Committees when evaluating research proposals (Beauchamp, 2019). For health research to be ethical, it is anticipated that participants and society's overall potential benefits will be greater than the risks to the individual research participant (Dhai, 2017). Therefore, for PGx research to meet the requirement of beneficence, the overall benefit to research participants and society must outweigh the risks to research participants. For this assessment, it is essential to note that risks are not limited to physical, but they can also include psychological and social risk.

The principle of beneficence is endorsed in all bioethics guidelines and declarations. Article 4 of the UNESCO *Universal Declaration of Bioethics and Human Right*s declares that "in applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximised and any possible harms to such individuals should be minimised" (UNESCO, 2005).

PGx research has the potential benefit of using genetic information obtained in health research and clinical trials to improve the safety and efficacy for research participants and society. As mentioned in chapter 2, PGx research can be advantageous in each stage of medicine advancement, from compound innovation to post-market observation. It can contribute substantially to promoting human health in South Africa (Peterson- Iyer, 2008). It can also positively affect future clinical medicine applications and contribute to creating medications to match each person on the grounds of their genetic structure (Tarantino et al., 2019). Consequently, when weighing up the potential risks and benefits of PGx research solely from a scientific and medical perspective, PGx testing risks seem minimal. The benefits to research participants and society are enormous. However, PGx research is not

without ethical and societal dangers, and before making an objective benefit-risk assessment, the following will have to be considered:

1) To what extent is widespread PGx research beneficial to research participants and society if the costs of personalised medicine will limit access to the wealthy (Morley & Hall, 2003)?
2) How will conflicts of interest in research be addressed to ensure researchers' potential financial gain in developing genomically tailored medicines will not negatively influence valid research and the best interest of research participants (Barash, 2001)?
3) Will research results be disclosed to participants? Many researchers agree that PGx testing results should not be given to research participants if there is no direct benefit to them. (Morley & Hall, 2003).

From a benefit-risk perspective, it appears that pharmacogenomics' primary objective is to benefit patient care by improving pharmacotherapy, alleviating risks of side-effects, and boosting patient and provider gratification by using personalised medicine. However, as seen above, several ethical challenges and concerns remain about the benefit of PGx research on research participants. Each scenario will have to be considered independently by health research ethics committees. The researchers must provide sufficient justification that the perceived risks related to PGx research are acceptable concerning the potential benefits to society. Comprehensive ethics guidelines and education of researchers, communities, and participants are essential as PGx research demand increases. If the ethical concerns can be dealt with, the idea that a person’s treatment will be directed by pharmacogenomics will become a reality (Hockings et al., 2020)

3.4.2 Non-Maleficence

Non-maleficence is complementary to the principle of beneficence. The principle of non-maleficence has its origin in the Hippocratic Oath, relates to the concept of harm, and is strongly linked with the maxim, *Primum non nocere* (above all do no harm) (Omonzejele, 2005). Non-maleficence advocates that one should not impose evil or harm. The duty of medical non-maleficence could be described as not imposing risks of harm and not doing actual harm. Therefore, the onus falls on the physician to maximise health and keep patients away from harm (Omonzejele,

2005). According to Beauchamp and Childress the rules of non-maleficence are as follows:

- Do not kill
- Do not cause pain or suffering
- Do not incapacitate others
- Do not cause offence to others
- Do not deprive others of the good of life (Beauchamp & Childress, 2013).

In practice, physicians frequently inflict harm on patients, but this is usually to do something good. Harm may be caused by prescribing chemotherapy to a cancer patient because of chemotherapy's serious adverse reactions. Still, in this case, the harm is justified to prevent death. This is also known as the use of double-effect medication, where harm appears to be in the patient's best interest (Omonzejele, 2005). However, the principle of non-maleficence demands that the unnecessary danger of harm is evaded, and when risk is unavoidable, the risk must be minimised as much as possible. Non-maleficence responsibilities are usually more demanding than beneficence responsibilities since a harmful action could get in the way of or impair a person's heath interest (Dhai, 2017).

In the health research context, if the proposed health research does not offer to improve the human condition by maximising benefit and minimising harm, then the research is unlikely to be ethical (DOH, 2015). Concerning PGx research, genetic sampling itself poses no more physical risk than a cheek swab or a blood test and appears harmless. However, harms can extend beyond the physical to social and psychological. Although Beauchamp and Childress emphasise the importance of bodily injury, they recognise the possibility of mental damage and admit that harms could expand beyond individuals to impact whole groups or societies (Beauchamp & Childress, 2013). Similarly, PGx requires looking further than the scientific knowledge gained from the research to the emotional and psychological aspects of human well-being.

The following are considered potential harms for research participants and communities participating in PGx research. The harms will not be discussed in detail in this section as it links with the principles of Respect for Persons, Distributive

Justice, and the Societal implications of PGx research, examined in subsequent sections and chapters:

- The most significant potential harm of PGx research lies in classifying a participant or community with limited healthcare access as 'non-responders' or 'poor responders' to a specific treatment (WHO, 2007; Peterson- Iyer, 2008). This may cause ethnic or racial stigmatisation or discrimination due to population or disease stratification, which may negatively influence specific population groups (WHO, 2007).
- Clinical trials with a PGx research component may include wide-ranging genetic information about research participants that may be entirely irrelevant to the original research objectives. It is doubtful that research participants will have considered the uses to which their genetic material might be put. Consequently, the process of informed consent may be confused by the unknown future uses of genetic information.
- The extensive collection and storage of genetic information present apparent issues about participant confidentiality and the level of anonymity of stored samples and raises the potential of harm due to unlimited or unlawful access to genetic information (Peterson-Iyer, 2008).

3.4.3 Distributive Justice

As a principle of ethics, justice relates to fairness, and in healthcare, it is associated with the fair treatment of patients. Distributive justice, as a notion of justice, relates specifically to the distribution of scarce resources. This principle acknowledges the need to treat all human beings equally without exploitation or deceit. Beauchamp and Childress define distributive justice as "*fair, equitable, and appropriate distribution of benefits and burdens determined by norms that structure the terms of social cooperation"* (Beauchamp & Childress, 2013).

With specific reference to healthcare, several contradictory theories on how to distribute scarce resources exist. These include:

Utilitarianism: Utilitarians support the greatest good for the most significant number of people and do what will have the best consequences for everyone concerned. In terms of this theory, if we need to decide what to do in a specific case, we merely calculate the outcomes of various actions and elect the one that brings about the

most significant benefit for the greatest number of people. It promotes public healthcare for as many people as possible (Kuhse & Singer, 2012; Beauchamp & Childress, 2013).

Libertarianism: This theory considers individuals as the fundamental unit of social consideration. Only individuals can make choices and are accountable for their acts. It suggests a social order in which individuals are free to follow their own lives on the condition that they consider others' equal rights. Libertarianism equates access to healthcare to those who can pay for it and consequently supports private healthcare (Boaz, 2019; Beauchamp & Childress, 2013).

Communitarianism: A philosophy whereby individuals' rights are submissive to the welfare of the community in which they live. It underscores the influence of communities in moulding individuals. This approach is widely held in Africa and is known as the philosophy of Ubuntu – "people are people through other people". According to this principle healthcare needs of a community must be prioritised over individual healthcare (MacIntyre, 1982; Beauchamp & Childress, 2013).

Egalitarianism: This philosophical theory maintains that human beings have intrinsic worth and should be treated equally. The goal of Egalitarianism is to generate the elimination of social inequity. Accordingly, all people should be entitled to the same distribution of healthcare, regardless of their ability to pay (Afolayan, 2015; Beauchamp & Childress, 2013).

The theories of utilitarianism, communitarianism, and egalitarianism all seem to support the principle of distributive justice. Limiting healthcare to those who can afford it (libertarianism) will not result in the fair distribution of limited resources and can, therefore, not be considered fair or just (Beauchamp & Childress, 2013).

South African healthcare is presented with critical challenges as a result of limited resources. According to the latest *General Household Survey*, conducted by Statistics South Africa: “only 17 in 100 South Africans are members of medical aid schemes, the essential key to private healthcare. As many as 45 million, or 82 out of every 100 South Africans, fall outside the medical aid net, and as a result, are primarily dependent on public healthcare” (Stats SA, *2016).* Consequently, health research and clinical trials, including PGx research, should aim to lessen the burden by ensuring that research participants and communities benefit from their research.

This position is supported in the South African Ethics Guidelines, which requires a fair balance between benefits and risks for all parties participating in health research, incorporating participants, societies, and the broad population. Specifically, it demands that the population from which health research participants are drawn should benefit from the research outcome, whether immediately or in the future (DOH, 2015). The principle of distributive justice in health research is also supported internationally in the CIOMS Guidelines, which states, "The equitable distribution of benefits and burdens in the selection of study populations requires that benefits of research be distributed fairly and that no group or class or persons bear more than its fair share of the risks or burdens from research participation" (CIOMS, 2016).

Concerning PGx research, topics related to distributive justice, which are widely debated, are access and benefit-sharing. Researchers or research sponsors can gain commercially because of their claims to ownership over human genes. This claim is based on the assumption that 'ownership' and other proprietary rights are feasible to genomic resources. However, this assumption is still widely disputed (see Chapter 4 below). Nevertheless, to ensure that research participants are treated justly and equitably, people who provide genetic material and data for research and development should be consulted, and they should give consent before their genetic resources may be accessed and utilised. Also, they should obtain acceptable compensation for their involvement. Where goods and resources are developed from genetic information, they should be distributed equally and fairly to research participants. The above translates into the concepts of access and benefit-sharing (WHO, 2007).

Applying distributive justice effectively in pharmacogenomics research is challenging when dealing with genetic diversity and different health needs across a variety of classes or groups. Public trust during the process of PGx health research design and implementation will play a fundamental role in safeguarding commitment and interaction of affected communities. There is an ethical duty on health care leaders fairly allocate limited resources. If resources are scarce, the community must be prioritised above the individual in fairly assigning limited resources. Once PGx therapeutics are available, limited quantities will be accessible due to scarce health

care resources. With this demand come the questions of who will be prioritised and how can we guarantee this distribution will be fair.

It is therefore particularly important for governments, researchers and other health care leaders to be transparent regarding the prioritising policies for providing treatments raise public awareness of why certain sub-groups of populations (e.g. populations with a genetic pre-disposition to adverse drug reactions) may be prioritised in the event of inadequate supplies. Without transparency about the distribution of benefits to research participants or communities, resentment, mistrust and a sense of exploitation will be generated. (Emanuel et al., 2004).

3.4.3.1 Access

On December 29, 1993, the United Nations Convention on Biological Diversity (CBD) came into force. It was motivated by the world's increasing dedication to sustainable development and had three key objectives (United Nations, 1993):

1. “The conservation of biological diversity.
2. The sustainable use of components of biodiversity.
3. The fair and equitable sharing of benefits arising out of the utilisation of genetic resources.”

Before the CBD, genetic resources were considered freely available, without the user's commitment to distribute benefits obtained from the genetic resources with providers or providing countries. The CBD altered this view by confirming that states hold an absolute right over their genetic assets (CBD, preamble, article 15). Genetic resources include both non-human (plant and animal) and human genetic resources (blood, tissue, etc.) (Dauda & Dierickx 2013). Articles 15(4) and 15(5) of the CBD subject access to genetic resources to prior informed consent (PIC) of the party making the resources available (provider) as well as mutually agreed terms (MAT). In terms of article 15(7), in return for access to the genetic resources, recipients of the resources must share benefits with the providers (United Nations 1993). "Access"' is not defined in the CBD but can be seen as acquiring samples of biological or other material, including genetic material within a country's border, with the aim of the research, conservation, commercial or industrial use.

A supplementary agreement to the CBD is the *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation* (hereafter Nagoya protocol) which was adopted on October 12, 2014. In addition to fair and reasonable sharing of benefits, the Nagoya protocol's objective also includes access to genetic resources. The Nagoya protocol provides a solid foundation for better legal confidence and clarity for both providers and recipients of genetic resources by expecting countries to create laws to guarantee that the utilisation of genetic assets is done with prior informed consent (PIC) and mutually agreed on terms (MAT). PIC is built on the principle that before obtaining access to genetic materials, those impacted and those sanctioned to make decisions should be informed about the possible uses of the materials to make a fully informed decision. This means that the provider must consent based on the potential recipient's information before the decision is made to grant access. MAT suggests a consultation between the groups providing access to the genetic resources and a body intending to utilise the resources, which usually leads to an access agreement or material transfer agreement (Gerber et al., 2012).

In South African legislation, "access" is established in chapter 6 of the National Environmental Management: Biodiversity Act of South Africa (10 of 2004) which outlines material transfer and benefit-sharing. The Bioprospecting, Access, and Benefit Sharing (BABS) regulations came into force on April 1, 2008, and the BABS Amendment Regulations entered into force on May 19, 2015. The BABS regulations regulate the notification process for the innovation phase of bioprospecting, including indigenous and genetic biological resources. Also, it specifies the permit system related to the export of indigenous genetic and natural resources from South Africa for bioprospecting or any other kind of research (Department of Environment, Forestry and Fisheries, 2019). The Biodiversity Act (BDA) and subsequent regulations only establish "access" in as far as it relates to non-human genetic material. It does not cover the vast assembly of human biological material from South Africa for research on deterrence, diagnosis, and treatment of illness (Mahomed & Sanne 2015;(Thaldar, Botes and Nienaber, 2020).

Nevertheless, South Africa has a well-developed domestic and legal setting dealing with human biological materials (HBM) for research and clinical trial purposes. In

terms of section 71 of the National Health Act of South Africa (61 of 2003) (NHA), written informed consent must be obtained from research participants before they participate in health research. Section 73(2) of the NHA also gives a mandate to Health Research Ethics Committees to confirm the proposed research meets ethical standards. The NHA Regulations relating to the use of Human Biological Materials (GN R177 GG 35099 of March 2, 2012), regulation 3(1)(a), further states that informed consent must be obtained from research participants for the utilisation of human biological material. Regulation 5 requires researchers who conduct research involving human participants must consult with representatives from the participating communities. Human biological materials (HBM) are not defined in the NHA. Still, in the regulations relating to the use of Human Biological Materials (2012), it is defined as “material from a human being including DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, small tissue biopsies and growth factors from the same”. This description, therefore, includes human genetic resources under the ambit of the NHA. The South African Ethics Guidelines state that it is the primary role of the HREC to protect the interest of research participants. However, it does not make specific reference to 'access' in terms of using human genetic materials (DOH, 2015).

In line with the Nagoya protocol requirements, the South Africa Minister of Health published a standard material transfer agreement (MTA) in the Government Gazette (4171 of July 20, 2018). The MTA stipulates that South African research institutions sharing human biological material for health research or clinical trials must have an MTA in place based on the published MTA template. This requirement is distinctive as it makes South Africa the only country to compel a standard MTA that obliges even parties (institutions) outside South Africa to use the MTA when transferring human biological materials to and from South Africa (Thaldar, Botes and Nienaber, 2020). The MTA reads as follows: “All the providers and recipients of biological materials for use in research or clinical trials under the auspices of Health Research Ethics Committees shall use the Material Transfer Agreement of Human Biological Materials” (Government of South Africa, 2018). In summary, the MTA must be used in all circumstances where HBM is relocated for research or clinical trials from a provider to a recipient. At least one of the parties must be situated in South Africa to place the transfer under South African jurisdiction. Paragraph one of the MTA

stipulates that the MTA does not need to be copied directly; however, it is not clear to what extent parties may deviate from the framework (Thaldar, Botes and Nienaber, 2020; Government of South Africa, 2018).

From the above, it is evident that an immense effort has been made to address the ethical and legal challenges surrounding the idea of access to HMB, including genetic materials. These efforts will ensure that everybody, including research participants and communities that provide genetic resources for research purposes, will be treated with the same dignity, respect, and moral worth as those who utilise these resources and is in agreement with the principle of distributive justice (Dauda & Diedrickx, 2013). However, there still seems to be a need to unify legislation, regulations, guidelines, and the MTA as far as access to HMB is concerned. No specific guidelines exist that directly address this issue.

3.4.3.2 Benefit Sharing

The concept of benefit-sharing is incorporated in the framework of access and the use of genetic resources. Both access and benefit-sharing link with the principle of distributive justice as it relates to the use of genetic resources in research. It deals with dignity, respect, and moral worth to those who provide these resources. In the structure of access and use of genetic resources, benefit-sharing is defined as "the action of giving a portion of advantages or profits derived from the use of genetic resources or traditional knowledge to resource providers to receive justice for the exchange" (Schroeder, 2007). From an international perspective, it can also be interpreted as what participants and communities in low-income countries should be given as a reward for their research participation (Dauda & Diedrickx, 2013).

The notion of benefit-sharing originates in the idea of humankind's common heritage whereby resources obtained from common heritage domains are not intended to be the property of individuals, communities, or states but has to be available for the rights and interests of all mankind (Dauda & Diedrickx 2013). For genetic and PGx research purposes, this idea suggests that the human genome belongs to all humans. Therefore, benefits derived from research should be for society's greater good, and those who directly contributed to the research should not derive any benefits (Mahomed & Sanne, 2015).

The concept of benefit-sharing in health research is not novel. It dates back to the *Declaration of Helsinki,* which states that “medical research in a vulnerable group is only justified if the research is responsive to the health needs or priorities of the group and the stand to benefit from the knowledge, practices, or interventions that result from the research” (WMA, 2013).

Article 15 of the UNESCO *Universal Declaration of Bioethics and Human Rights* provides clear explanations of the concept of benefit-sharing, and the different forms that benefits may take. This article reads as follows:

1. “Benefits resulting from any scientific research and its application should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefit may take any of the following forms:
    (a) Special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;
    (b) Access to quality health care;
    (c) Provision of new diagnostics and therapeutic modalities or products stemming from research;
    (d) Support of health services;
    (e) Access to scientific and technological knowledge;
    (f) Capacity building facilities for research purposes;
    (g) Other forms of benefit consistent with the principles set out in this Declaration”.

(UNESCO, 2003).

The Council for International Organisations and Medical Sciences (CIOMS) *International Guidelines for Biomedical Research Involving Human Subjects* was developed in conjunction with the World Health Organisation (WHO) in 1993 and last updated in 2016. These guidelines give support for benefit sharing and state that research in low-income countries and communities should leave the research participants better off than in the past or at least no worse off (Mahomed & Sanne, 2015). Guideline 2 deals specifically with research conducted in low-resource settings and requires that research must meet the particular needs of the community

in which the research is conducted. Every attempt must be made to make available any invention, product, or information that results from the study to the research community. It further states that benefits do not only include interventions or products but can also include capacity building and investments in local health infrastructure (CIOMS, 2016). Guideline 3 addresses the reasonable allocation of benefits and burdens in selecting people and communities of research participants. In line with the principle of distributive justice, this guideline requires that research stakeholders must warrant that the benefits of research are reasonably distributed, by not focussing disproportionately on the requirements of a small class of people, but aim to deal with different health needs across a variety classes or groups (CIOMS, 2016).

As mentioned previously, the Nagoya protocol provides for the successful execution of fair and equitable benefit sharing from genetic resources. Of note is the specific reference to genetic resources, which has been absent from earlier guidelines. Article 5 deals specifically with fair and equitable benefit sharing and stipulates that indigenous and local communities are expected to consent and agree on mutual terms related to the use of genetic resources. Each party to the protocol must take administrative, legislative, or policy actions to guarantee that benefits are allocated fairly and justifiably with the party who supplies the resources (Mahomed & Sanne 2015). Also, it states the benefits can include monetary or non-monetary benefits. In terms of article 8 (b) of the Nagoya Protocol, "In the development and implementation of its access . . .legislation or regulatory requirements, each party shall pay due regard to cases of present or imminent emergencies that threaten or damage human, animal or plant health as determined nationally or internationally. Parties may take into consideration the need for expeditious access to genetic resources . . ., including access to affordable treatment by those in need, especially developing countries" (Convention for Biological Diversity, 2011).

Due to South Africa's genetic diversity, large-scale HBM is collected for purposes of PGx research. The South African research community is part of various projects that include sharing HBM and associated data, including genetic data for research. Benefit-sharing is the process whereby benefits of the research outcome can be

shared fairly and equitably for those who contributed to the research (Thaldar, Botes and Nienaber, 2020).

The South African Biodiversity Act (10 of 2004) is the only legal document that indicates what a 'benefit' may involve for bioprospecting or any other type of research involving indigenous biological resources. However, as mentioned in preceding sections, the Act excludes human genetic materials from its application. The Act provides for “sustainable utilisation of indigenous biological resources and the fair and equitable sharing of benefits resulting from bioprospecting or including indigenous biological resources”. Section 1 of the Act defines benefits concerning bioprospecting involving indigenous biological resources as “any benefit, whether commercial or not, arising from bioprospecting involving such resources, and includes both monetary and non-monetary returns". Section 82(2)(b) makes it mandatory for the recipient and provider (a person, community, state) of the resources to enter into a Material Transfer Agreement. The MTA must standardise the provision of access to resources as well as a benefit-sharing agreement. Section 83 of the Act requires that the benefit-sharing agreement must specify “the type of indigenous biological resources to which the relevant bioprospecting relates; the area or source from which the indigenous biological resources are to be collected or obtained; the quantity of resources to be collected or obtained; and any traditional uses of the resources by an indigenous community”.

The South African Ethics Guidelines state the following concerning distributive justice “there should be a fair balance of risks and benefits amongst all role-players involved in research, including participants, participating communities, and the broader South African society. In this way, the principle of equality is expressed in the research context. No segment of the population should be unduly burdened by the harms of research or denied the benefits of knowledge derived from it. There should be a reasonable likelihood that the population from which participants are drawn will benefit from the research results, if not immediately, then in the future.” In section 2.3.1, the Guidelines specify that the research should be relevant and responsive to South Africa's needs. This requires that research proposals describe the anticipated contribution to knowledge creation and, ideally, how the results might be transformed into commodities, inventions, processes, or amenities likely to

enhance living standards and South Africans' well-being (DOH, 2015). Although the Guidelines address donation of human biological materials, genetic and genomic research, it does not address the concept of benefit-sharing in direct application to these subjects.

The South African MTA defines benefit-sharing as “the process or act of sharing in the benefits derived from the Project in a fair and equitable manner”. It also requires that benefit-sharing between Provider and Recipient must be “discussed and negotiated” before any material may be conveyed to the recipient. However, there is no clear clarification of what is proposed with 'discussed and negotiated', which may raise the question of whether a benefit-sharing agreement is compulsory. Furthermore, it is unclear what a benefit-sharing agreement between a Provider and Recipient should incorporate (Thaldar, Botes and Nienaber, 2020).

Preceding chapters support the likelihood that PGx research will add to the relief of suffering of people with severe disease and disabilities. Human genetic materials collected for research purposes from participants or communities may positively impact the development of new medicines, from interventions that benefit the whole of humanity to treatments or remedies for participants with a specific medical condition. However, these discoveries may not necessarily result in direct medical benefits for people or the individual from whom the samples were obtained. For example, a family with a rare genetic disorder may provide tissue samples for PGx research, leading to medicine development. Still, this medicine may not be of any direct therapeutic benefit to the family, and public healthcare providers in resource-poor settings may not be able to afford the costs of this medicine. Furthermore, it may take many years to develop new interventions based on the human genetic materials collected from a specific participant or population (Wertz, 2011). Therefore, in low-income countries with limited resources and access to healthcare, the notion of common heritage could result in serious ethical concerns about the exploitation of research participants and communities. There may be little or no direct benefit to these communities in the future (Mahomed & Sanne, 2015). There is also the risk of biopiracy, whereby researchers acquire genetic resources without obtaining permission or sharing benefits with host countries or local communities, which goes against the principle of distributive justice (Dauda & Diedrickx, 2013).

The concept of benefit-sharing should move from local or individual benefit to a wider or population-based benefit. This more comprehensive view of benefit-sharing can include technology transfer, local education, providing healthcare or knowledge structures, or using percentages of royalties for charitable purposes. By returning a percentage of profits generated by PGx research to communities who have taken part in the research, it is possible to benefit the community without locating individual participants and thereby avoiding concerns related to the body's commodification. Concerning the principle of distributive justice, providing a proportion of earnings to populations who took part in the PGx research seems reasonable on the ethical foundation of an obligation to those in need (WHO, 2007).

From the discussion above, it is clear that the idea of benefit-sharing has gone through a fundamental ethical and legal transformation from its origin in the common heritage of humankind to its application in international research. It has moved from the principle of justice as equal opportunity whereby everyone has the right to dignity, respect, and moral worth to the principle of justice in exchange, which requires that fairness is guaranteed in what is traded when countries relate. When participants, communities, and populations donate genetic samples for research, sponsors should distribute the benefits of the research to those participants, communities, and populations (Dauda & Diedrickx, 2013). However, despite local and international protocols, declarations, acts, and guidelines addressing the concept of benefit sharing, indigenous genetic resources, and human genetic resources, no clear guidelines exist in South Africa that speaks to benefit-sharing related to PGx testing in research or clinical trials. Guidelines for PGx research on HBM must formulate benefit-sharing in such a way that the quantity of benefits accumulated from research participation is matched with a minimum standard of benefits provided to the collaborating community. Local guidelines will drive international researchers to accept the benefit requirements whenever they interact with local research communities, encouraging communities to collaborate in research and dissipate mistrust issues (Dauda & Diedrickx 2013). Ethics guidelines must consider that benefit-sharing arrangements may be difficult and challenging and must therefore prescribe the involvement of communities, Research Ethics

Committees, governments and researchers before initiating research (Warnich et al. 2011; Mahomed & Sanne, 2015).

3.4.4 Respect for Persons (Dignity and Autonomy)

Traditionally, the physician-patient relationship was interpreted as a paternalistic one where the physician made a choice and the patient deferred to it. In recent years, with the development of the concept of human equality in terms of human rights, this interpretation has been rejected, and the conviction is that all human beings deserve respect and equal treatment (WMA, 2015).

Respect for persons promotes the individual as an autonomous being, competent to make individual choices and decisions. Autonomy means 'self-rule' and is linked to freedom of choice and people's capability to make their own decisions grounded on options presented to them. Autonomous human beings must make subjective decisions that consider their values, opinions, standards, and beliefs. Respect for autonomy incorporates all elements that affect an individual's decision-making capacity. In *A Companion to Bioethics,* Kuhse and Singer (2012: 530) quote Isaiah Berlin (1969) as follows: “I wish my life and decisions to depend on myself, not on external forces of any kind. I wish to be the instrument of my own, not of other men's, acts of will. I wish to be a subject, not an object … I wish to be somebody, not nobody. I wish, above all, to be conscious of myself as a thinking, willing, active being, bearing responsibility for my choices and able to explain them by reference to my own ideas and purposes”. This quote underpins the concept of autonomy (Kuhse & Singer, 2012).

In health research, autonomy calls for research participants, who can make their own choices, to be treated with respect and allowed to reflect on a decision and act on that decision by exercising the freedom to give voluntary, informed consent. Respect for persons also acknowledges the dignity, well-being, and safety of research participants. Therefore, for those individuals with diminished capabilities to give informed consent, extra protection must be provided to protect them from the risk of harm (Kuhse & Singer, 2012). Respect for persons requires that the interests of participants should outweigh the interest of science and society. This is in line with what is proposed in the *Declaration of Helsinki* (WMA, 2013). Respect for persons

also requires that the confidentiality of research participants is respected. Moreover, respect for persons advocates that researchers' interests, such as authorship and intellectual property, must be respected (DOH, 2015). Respect for autonomy is not unqualified. It must be adhered to only if it does not contradict an equal or stronger principle. Autonomy establishes the following obligations:

1. Informed consent
2. Confidentiality
3. Truth-telling
4. Effective communication

(Moodley, 2017).

For purposes of this research report, I will focus specifically on the obligations of informed consent and confidentiality as it relates to PGx research.

3.4.4.1 Informed Consent

In the healthcare environment, patients act autonomously when choosing (all things considered) which alternatives for dealing with a health problem will be best for them. Informed consent, therefore, acknowledges the value of the participant's autonomy (Kuhse & Singer, 2012). In health research, the first international document to acknowledge informed consent was the Nuremburg Code (1947). After that, it was included in most guidelines and regulations dealing with the conduct of health research in human participants and has become the trademark of Western bioethics (Nuffield Council, 2003). Voluntary informed consent must be obtained from all participants taking part in health research unless there is a lawful reason for not doing so. Informed consent is a continuous process and starts before any research procedures may be conducted on a participant and should continue throughout the study.

For research participants to give informed consent, they must be competent, understand the information given to them, be conscious of the significance of the information, and give consent freely (Kuhse & Singer, 2012). Firstly, it is critical to determine if a participant is competent to consent. Competence requires the capacity to communicate a decision, comprehend the information given, be aware of the possible consequences of research participation and rationalise the decision to

participate in research (Moodley, 2017). Secondly, the participant must understand and be conscious of the information provided. In this case, the importance should not be on what was disclosed but on what the participant comprehended. The researcher must attempt to promote understanding. Thirdly, consent must be given freely. Suppose consent is given as a consequence of coercion or unjustified influence. In that case, it cannot be considered valid consent, even if the participant is provided with all the relevant information and comprehends and appreciates the information (Kuhse & Singer, 2012).

The concept of informed consent for participation in health research in South Africa does not merely rely on international guidelines and declarations but is entrenched in local legislation. Section 12(2) of the Bill of Rights in the SA Constitution protects against research abuse by providing that “everyone has the right to bodily and psychological integrity, which includes the right –
(a) to make decisions concerning reproduction;
(b) to security in and control over their body; and
(c) not to be subjected to medical or scientific experiments without their informed consent” (Act 101 of 1996). Furthermore, in terms of Section 71 of the National Health Act of South Africa (61 of 2003), health research may only be conducted on human participants with the written consent of the participant. The South African *Guidelines for Good Practice in the Conduct of Clinical Trials in South* Africa (1996) defines informed consent as “A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented utilising a written, signed and dated informed consent form” (DOH, 2006). Section 2.3.6 of South African Ethics guidelines read as follows: “In general, participation in research must be voluntary and predicated on informed choices. Voluntariness and informed choices are evidenced by the informed consent process which must take place before the research commences, in principle, and be affirmed during the study, as part of the commitment to an ongoing consent process” (DOH, 2015)

Consent for PGx research allows researchers to connect genetic research on samples obtained during a clinical trial to the research participant's personal medical

information. This practice differs from conventional clinical trials where participants can benefit from interventions under study, comparator medications, or study procedures. There may be no direct benefit for PGx research participants even if the investigation leads to future benefit for society. Samples may even be used for research not related to the initial clinical trial (Corrigan, 2005).

Due to the unconventional nature of PGx research, various concerns exist around obtaining fully informed consent from research participants. In 2003, the Nuffield Council on Bioethics published a report on ethical issues in Pharmacogenetics. In this report, the Nuffield Council questioned whether research involving PGx testing can ever truly be voluntary since participants frequently agree to participate in clinical research as it may be the only opportunity to get access to a specific medication. The PGx research component is often an additional component of clinical trials. Participants likely feel they have to participate in the PGx part to qualify for the main clinical trial. In low-resource settings, where access to healthcare is limited, this raises the concern around free, voluntary informed consent specifically for the PGx component of health research (Nuffield Council, 2003). To this effect, CIOMS published *Pharmacogenetics: Towards improving treatment with medicines* in 2005. In this publication, the authors stressed that participation in a clinical trial should not be subjected to involvement in the PGx component of a clinical trial unless PGx test results are part of the clinical trial selection criteria. The authors recommend that where clinical trials involve a PGx element, separate informed consent should be obtained. In this manner, all information about the PGx research is in a free-standing document to ensure participants' participation in the clinical trial can proceed without involvement in the PGx study (CIOMS, 2005). The requirement for separate informed consent for optional PGx research is still widely used by HRECs today. This practice allows for awareness by participants that partaking in the clinical trial component does not depend on participation in the PGx research component. They will be allowed to participate in the main clinical trial without participating in the PGx component. This practice contributes to the voluntariness of the consent.

A further concern related to informed consent for PGx research is the potential that participants will not truly understand the study's scientific nature. Research participants must be fully informed of the possible uses of their genetic information

before they consent to testing (WHO, 2007). They should also be advised that they may be expected to disclose this to insurers and employees once their genetic information is acquired. Furthermore, participants must be aware that PGx tests will disclose information about themselves and other family members. In low-resource countries and vulnerable communities, where literacy levels may be low, it can be highly challenging for participants to understand these concepts (Morley & Hall, 2004). In addition to the issues of limited literacy or education, issues such as language barriers, belief systems, and cultural and traditional sensitivities may also influence communication between researchers and participants, which may undermine the principle of truly informed consent (Warnich et al., 2011).

A third concern relates to informed consent for future research on human biological materials (HBMs) as researchers discover more about the human genome (Peterson-Iyer, 2008). The type and restrictions of consent can determine what may be done with a sample to a certain extent. Guideline 11 of the 2016 CIOMS guidelines deals with collecting, storing, and using biological materials and related data. In terms of this guideline, human biological materials can include tissues, organs, blood, DNA, and RNA that may be collected for specific research or future research even though the research's specifics may not be known at the time of consent. The guideline focuses on biobanks and storage of HBMs and requires that research participants whose materials are stored must unequivocally authorise future use. Even though no specific mention is made to PGx research samples, we can assume that the guideline incorporates PGx research that may be conducted on stored samples in the future.

In the commentary on Guidelines 11, provision is made for two types of informed consent, namely specific informed consent and broad informed consent. If it has been determined what the samples will be used for during sample collection, explicit informed consent must be obtained for predetermined tests conducted for one research study or research related to one medication type (CIOMS, 2016). However, this type of consent poses fundamental limitations to PGx research, where the research could potentially be conducted several years after the initial study. PGx research may include questions and methods that could not have been foreseen at the time of sample collection and require a careful balance between autonomy and

the public good. PGx research benefits may affect the societal interests of scientific innovation that is much wider than diagnosis, prevention, and treatment of disease (Dhai, 2017). In those instances, guideline 11 suggests that broad consent can be obtained. The donor or research participant permits the samples to be used for the current research protocol and for storage and possible future research for which the nature of the research may be unknown at present. In a broad consent, the type of further use should be as detailed as possible and should specify that prior ethics approval of any new research must be obtained. Permission may be required to re-contact the participant if the planned future usage is not within the existing consent scope (CIOMS, 2016).

The South African Ethics Guidelines expand on the provisions of guideline 11 by adding tiered consent, which is where the donor gives consent for the main research and decides whether to allow storage for future use (DOH, 2015).

It is important to note that broad consent is not blanket consent that allows future use of samples without any limit. Broad consent puts specific restrictions on the future use of biological materials, such as conditions and duration of storage, how the donor can get in touch with the biobank, and the intended use. Blanket or open consent is not proposed for PGx research due to hereditary elements in multicultural societies. These elements suggest that samples can be re-identified, even if only to a group or community rather than an individual, and may impact the principle of respect for persons if confidentiality cannot be maintained (DOH, 2015).

Although ethical guidance places considerable emphasis on written consent, making provision for the consent process to be adequately monitored and documented should be as important as having a written informed consent document, especially in those communities where literacy and understanding of science are limited (WHO, 2007). This does not imply that informed consent should not be appropriately obtained and recorded but allows the format to vary. Where research information is provided to participants with little or no literacy, the language must be a language that participants understand. The participant's level of comprehension must be assessed before consent is given. The use of analogies, illustrations, and pictographs can be helpful to explain scientific concepts. The idea of research, as

opposed to healthcare, may also be alien to participants, and therefore, consideration should be given to providing information in different ways. The utilisation of community meetings, healthcare workers, or appropriate media can be considered (WHO, 2007).

Notwithstanding the above concerns related to the nature and type of informed consent, it is common practice to require explicit informed consent before obtaining PGx research samples. As with all health research, the nature and implication of the research (as specified by the CIOMS guidelines) must be explained to prospective participants. Unfortunately, the information provided in informed consent documents is never entirely comprehensive, and descriptions are often misunderstood, and inventing a more detailed consent form will not solve this problem. The Nuffield Council on Bioethics states the following in this regard: "Fully informed consent is, therefore, an unobtainable ideal. Obtaining genuine consent requires medical practitioners to do their best to communicate accurately as much as patients, volunteers or relatives can understand about procedures and risks and to react to the limits of their understanding and their capacities to deal with difficult information. If all reasonable care is exercised, adequate and genuine consent may be established, although it will necessarily fall short of fully informed consent" (Nuffield Council, 2003).

Ethics guidelines for consent in PGx research need to identify the essential elements for written informed consent for PGx research. Still, it must also make provision for circumstances where participants' literacy levels may be low and where it may be difficult for participants to understand the science behind PGx and sample storage.

3.4.4.2 Privacy and Confidentiality

Privacy is a legal right to which patients and health research participants are entitled and is defined as a research participant's interest in controlling access to their personal information (DOH, 2015). Protection of participant's personal information is, accordingly, a legal obligation (ASSAF, 2018). Upholding confidentiality in the doctor-patient relationship is a long-standing moral duty preserved in the Hippocratic Oath, as stated in the Declaration of Geneva (WMA, 1948) and other codes of conduct. Confidentiality in health research refers to how research data might be disclosed, thereby revealing the participant's identity and making them susceptible to

harm (DOH, 2015). In health research, confidentiality is upheld as far as possible, but at a more subtle level considering the variety of interested parties in health research. Nevertheless, health researchers are bound by the duty of confidentiality (ASSAF, 2018).

In the *Casebook on Ethical Issues in International Health Research*, the WHO divides privacy interests into three categories:

> "1. Control over who has access to information about someone (e.g. whether they have the gene for severe and adult-onset disease). This control extends not only to which people have access to the data but also how much access individuals are willing to provide to others, and when and under what circumstances they are willing to do so;
> 2. Control over who has the right to observe someone when they are not in a public space (e.g. a doctor might be allowed to examine someone medically, but others who might have a legitimate interest in observing that examination, such as medical trainees or researchers might not);
> 3. Control over specific decisions concerning oneself (e.g. women's decisions about whether to have children)" (WHO, 2009).

Article 9 of the Universal Declaration of Bioethics and Human Rights states that: "The privacy of the persons concerned, and the confidentiality of their personal information should be respected. To the greatest extent possible, such information should not be used or disclosed for purposes other than those for which it was collected or consented to, consistent with international law, in particular, international human rights law" (UNESCO, 2005). Article 3 of the International Declaration on Human Genetic Data reinforces the principle that a person's identity should not be condensed to genetic traits. Personal identity includes various intricate factors, such as education, environment, emotions, culture, etc. In article 4, human genetic data is given special status since it can project genetic tendencies, may have considerable influence on families and communities, may hold information of which the importance is unknown at the time of collection, and may have cultural implications for individuals and communities. Due to the special status given to human genetic data, special attention should be given to this data's sensitivity, and appropriate measures should be put in place to protect the information (UNESCO, 2003).

The World Medical Association general assembly adopted the *Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks* in Taipei, Taiwan, in October 2016. The Declaration sets ethical principles for medical research involving human participants, including the significance of protecting the dignity, autonomy, privacy, and confidentiality of research participants and obtaining informed consent for using identifiable human biological material and data. The Declaration acknowledges that the dignity, autonomy, privacy, and confidentiality of research participants must be respected and that parties responsible for conducting research must act as stewards in protecting the information provided by participants. It also states that these rights entitle participants to exercise control over the use of their data and biological materials. Paragraph 10 emphasises that confidentiality is crucial for maintaining trust and integrity, and knowing that their privacy will be respected assures participants when sharing sensitive personal data (WMA, 2016). Even though the Declaration does not deal specifically with genetics and pharmacogenetics, it relates to the use of HBM, which includes genetic materials.

In PGx research, a blood or tissue sample is often the only physical involvement of a participant in the research's PGx component. The sample is consequently a vital connection between the participant, the participant's medical records, and the PGx research results. How samples are stored, coded, archived, transferred, and results disclosed, is critical if the research goals are to be achieved. Where participants fear public disclosure of information, enrolment and retention in the PGx component of the research may be difficult. Various types of PGx research exist, and therefore, it is likely that risks related to privacy and confidentiality will differ. As with all genetic data, PGx research risks exist due to the familial and social nature of genetic information. Preserving a link between participants who donate blood for PGx research and their personal information may result in discrimination and stigmatisation. For example, PGx may disclose information such as disease susceptibility that may result in social exclusion or bias. In contrast, information about the genetic make-up of a specific population may pose a risk to that population (WHO, 2007).

Sponsors, researchers, ethical, regulatory, and scientific bodies dealing with PGx in clinical trials must have a common understanding of the language which describes sample collection and handling. In support of this endeavour, the US Department of Health and Human Services, Food and Drug Administration, published the *Guidance Document: E15 Pharmacogenomics Definitions and Samples Coding,* in April 2008. This document provides terminology that can be used in relation to the collection of human samples for genetic research. They define the following five categories for labelling and coding of genetic samples:

1. Identified Samples/Data: Labelled with personal identifiers such as name, date of birth, or identity number. The sample and related data can be traced right back to the donor with a direct link between the participant's identity and the PGx results/data. The participants' records are identifiable for clinical monitoring, and the samples can be withdrawn with immediate effect. Results of identified samples can be returned to the individual participant, but it offers little privacy to the participant. This category is similar to confidentiality in the standard healthcare setting (US FDA, 2008).
2. Single-Coded Samples/Data: Labelled with a participant code that can be linked back to the participant by the investigator. The sample does not contain any personal identifiers. This practice is similar to the conventional clinical trials approach and includes a step to separate the participant's identity from the results. The investigator does not have immediate access to the participant's identity, but it can be disclosed by breaking the code. Data can be monitored and audited for regulatory purposes, and it is possible to withdraw the sample or data or update participant information. It is also possible to return individual results to the participant (US FDA, 2008).
3. Double-Coded Samples/Data: Double-coded and labelled with a unique second code. A link is retained between the participant code and the unique second code but is unknown to the investigators and participants. Samples are void of any personal identifiers. This additional privacy protection ensures that anyone with access to the genetic results can only track the participant's identity to a coded identifier. A further key is necessary to link participant identifiers with genetic information, making it possible to return individual results to a participant in exceptional circumstances. It is also possible to monitor and audit the study and withdraw samples through a precise protocol

procedure that must also be included in the informed consent document (US FDA, 2008).

4. Anonymised Samples/Data: Double-coded and labelled with a unique second number where the link between the participant number and the unique second number is deleted. Once the link is deleted, it is impossible to link a participant's identity with genotyping results. It is no longer possible to monitor and audit the study, withdraw samples, or provide participants with results. Anonymisation offers the most significant possible level of protection for comprehensive genotype-phenotype correlative analysis. It contains no personal data or clinical information that might result in tracking the identity of a participant. There is no possibility to trace the genomic data and sample to a specific participant. However, some data can be linked with anonymous samples, such as certain medical conditions, age, and sex (US FDA, 2008). The idea of irreversible anonymisation of samples is not unqualified. DNA samples can never be completely anonymous due to hereditary elements in the samples or data (ASSAF, 2018).

The decision on which level of privacy protection to use for PGx research depends on the type of research, the proposed use of the sample/data, the aim of the research, and country-specific legal and regulatory requirements. The implications for participants who provide PGx samples for health research will vary depending on how easy it is to link the participants to the samples and influence whether a participant decides to participate in the research, which may consequently influence enrolment in a clinical trial. The greatest privacy protection is provided to anonymised samples, but this may result in participants not having access to research findings, inability to verify participant data, and participants' inability to withdraw consent (WHO, 2007). Furthermore, in clinical trials that continue over a long period, anonymisation may compromise the research goals. There may be data verification requirements from regulators that demand that samples cannot be anonymised. It is suggested that storing samples in a coded or identified form may be adequate when participants know the exact type of research to be conducted. It is important to remember that genetic markers make it possible to identify groups or communities irrespective of whether the samples are de-identified. Therefore, unspecified use of samples for genetic testing is not recommended, and a limitation

should be put on the type of research conducted on the samples (Nuffield Council, 2003).

Privacy and confidentiality of genetic information are essential priorities in jurisdictions that control the release of and access to personal information. From a South African perspective, Section 14 of the Bill of Rights of the Constitution of South Africa Act (101 of 1996) confirms the right of all individuals to privacy and the right not to have the privacy of their communications infringed. Until June 2020, information related to research was regulated by the following:

- Section 14 of the National Health Act of South Africa deals specifically with health information (Act 61 of 2003).
- The Promotion of Access to Information Act (Act 2 of 2000).
- *Ethics in Health Research: Principles, Processes and Structures* (DOH, 2015).

This changed with the coming into force of the Protection of Personal Information Act (POPIA) (4 of 2013) on July 1, 2020. All public and private bodies dealing with personal information have until July 1, 2021, to ensure compliance with this law. The purpose of POPIA is predominantly to give force to the constitutional right to privacy by protecting personal information when processed by a 'responsible party' and standardising how personal information may be processed legally and in line with international standards. For purposes of POPIA, “processing” is defined as, among others, “collections, storage, use dissemination, distribution, and destruction of information”. “Personal information” is defined as, among others, “physical or mental health information and biometric information, which incorporates DNA analysis” (Act 4 of 2013).

Data linked with human biological materials in the ambit of health research would, in all probability, be covered by POPIA (Thaldar, Botes and Nienaber, 2020). POPIA further requires that personal information be processed according to eight conditions: “accountability, processing limitations, purpose specification, further processing, information quality, openness and transparency, security safeguards, and data subject participation” (Act 4 of 2013). For this report's purposes, I will focus on the 'processing limitations', 'purpose specification', and 'further processing' conditions.

The “processing limitation” condition requires that personal information be processed only if a legal ground for processing is present. Consent by the data subject is the legal ground applicable for health research data to be processed(s9-12). In section 1 of POPIA, consent is defined as “any voluntary, specific and informed expression of will in terms of which permission is given for processing personal information”. The 'purpose specification' condition specifies that personal data “must be collected for a specific explicitly defended purposes” (s13). Thirdly, the “further processing limitation” stipulates that there can be further processing of personal information if further processing is for research objectives. This stipulation is conditional upon further processing being performed exclusively for research purposes, and the personal information may not be published in any identifiable form (s15) (Act 4 of 2013). Section 26(a) of POPIA states that personal information concerning, among other things, health or biometric information is considered unique personal information and may not, subject to section 27, be processed. Section 27 states that the prohibition in section 26 does not apply if the said processing is carried out with consent (s27(1)(a)), is for research purposes and serves a public interest, or it is impossible or involves disparate effort to ask for consent, and assurance is provided that the processing does not negatively influence the personal privacy of the data subject (s27(1)(d).

In summary, genetic samples and data (including PGx research samples and data) can be considered 'personal information' in terms of POPIA. Accordingly, this information may be collected if *the research participant provides voluntary, specific, informed conse*nt. Genetic samples and data can also be considered 'special personal information' that can be processed with *voluntary, explicit consent* or if the processing is for research purposes and corresponds with s27(1)(d)(i) and (ii) conditions (POPIA). For both personal and special personal information, specific consent is required for processing. Yet, for special personal information, it seems as if consent is not required under the conditions of s27(1)(d) as long as the research participant is not negatively affected. To this effect, some would argue that a 'specific' expression of will should instead be amended to a 'broad' expression of will. However, section 37 of POPIA provides for an Information Regulator (IR) that can relieve persons from the eight provisions for the processing of personal information,

and the decision should therefore be left to the IR to decide on an exemption for persons engaging in health research, including PGx research (Thaldar et al., 2020).

Irrespective of the protection that POPIA offers health research participants concerning their genetic data, it is essential to note that POPIA contains a one-year grace period. Its implementation period will only be from July 1, 2021. Consequently, it is vital to ensure continuous compliance with the Department of Health Ethics Guidelines, which deals specifically with privacy and confidentiality in health research in section 3.1.8 (DOH, 2015). The guidelines do not make specific reference to privacy and confidentiality as it relates to human biological materials or PGx samples obtained for health research. However, it encourages Health Research Ethics Committees to give careful attention to measures to protect research participants' privacy and confidentiality and provide specific terms on how this should be done (DOH, 2015). The South African Ethics Guidelines devotes a section to data and biological materials for research purposes. It recognises that genetic markers collected for health research purposes can potentially identify groups even if it was anonymised to such an extent that it cannot identify individuals. It further recognises that complete anonymisation is not necessarily the answer when collecting genetic samples as it may inhibit the disclosure of essential findings to research participants and communities (DOH, 2015). However, the above guidelines do not give any specific guidance regarding the various sampling categories concerning PGx samples in health research.

It is recommended that Guidelines for Ethics in PGx research incorporate the provisions of POPIA with clear explanations on the uncertainties in the act while keeping in mind the basic principle of respect for persons as far as it relates to informed consent and the protection of personal information of the research participant.

While the way in which PGx samples are being handled, analysed, and coded may depend on the type of PGx research that is being undertaken, the management of the PGx samples and data must be conducted in such a way as to protect the privacy and confidentiality of research participants as far as possible, taking into consideration the particular requirements of the PGx research (WHO, 2007).

3.5 Conclusion

This chapter aimed to explore the concept of health as a fundamental human right as it relates to Pharmacogenomics (PGx) research. A further objective was to identify the relevant ethical principles in doing health research and then applying them to PGx research in South Africa. A broad overview was provided on the basic principles of beneficence and non-maleficence, distributive justice, and respect for persons. Further attention was given to access, benefit-sharing, consent, and confidentiality as they relate to the principles of distributive justice and respect for persons.

It can be concluded that it is possible to apply the basic ethical principles in PGx health research. Nevertheless, it is crucial to apply these principles to the unique challenges posed by PGx research and, in particular, PGx research in low resource settings such as South Africa. The principles of distributive justice (access and benefit-sharing) and respect for persons (informed consent and confidentiality) are sensitive issues in this environment. They should receive special attention in the conduct of PGx research in South Africa.

CHAPTER 4: LEGAL IMPLICATIONS OF PHARMACOGENOMICS (PGx) RESEARCH

4.1 Introduction

The main legal challenges surrounding PGx research focus on the ownership of genomic resources and the information derived from the research conducted on genomic resources (Rhodes, 2015). In this chapter, I will examine the five approaches towards ownership of genetic resources and consider potential solutions to the contradictions and uncertainties associated with this topic, employing local legislation, regulations, and international case law. Lastly, I will discuss the role of patents and international property rights in PGx research.

4.2 Ownership of Genomic Resources

One of the most frequently disputed questions in genomic and PGx research is whether genomic resources can be owned. Recent deliberations seem to assume, without justification, that 'ownership' and other proprietary rights are feasible to genomic resources, but no clear guidance to this effect is offered (ASSAF, 2018)

Internationally, there seem to be five approaches towards ownership of genomic resources:

1. Free Access: Anyone is free to access, use and demand property rights over genomic resources. This approach was the leading international view before applying state sovereignty rights and is inclined to support those who have specific expertise, monetary and technological means to obtain and utilise the resources. Therefore, access is limited to a small group of individuals, communities, and countries, irrespective of where they are sourced (Rhodes, 2015).
2. State Sovereign Rights: In terms of Article 15 (1) of the Convention of Biological Diversity, “the authority to determine access to genetic resources rests with the national government and is subject to national legislation” (Secretariat of the CBD, 1993). This approach gives the right to determine what happens to genomic resources to the country's government from where the resources were obtained. However, it does not declare that the state owns the genomic resources. Therefore, it does not exclude future claims of intellectual property claims made by the user or recipient (Rhodes, 2015).

3. Intellectual Property Rights: The type of intellectual property right that can be asserted over human genomic resources is patents. Patents are progressively being claimed over a significant variety of genetic resources. Intellectual property rights and patents will be discussed in detail in section 3 of this chapter.
4. Common Heritage of Mankind: The concept of the common heritage of mankind (as discussed in chapter 3) developed from the creed of *res communis.* This creed sets out that resources acquired from common heritage terrains are not meant to be exploited, acquired, or owned by people, communities, or states. The use of such resources has to be available for all of humankind's rights and interests (Mahomed & Sanne, 2015). Applying this concept to genomic resources would mean that the resources would be governed in line with universal claims, and any benefit resulting from their use would be shared internationally (Rhodes, 2015).
5. Mixed Systems: This system merges state sovereignty and benefit-sharing structures components with some intellectual property rights allowance.

The approaches mentioned above provide a range of options for the international community concerning human genomic resources governance. Until an agreement is reached on a single global strategy, the likelihood is that governance will fall back on free access and promoting the advantage of selected groups over others. It will also indicate that choices on which research priorities are engaged will be based on global significance and not national significance and commercial capacity (Rhodes, 2015).

Traditionally, South African law does not acknowledge biological samples as property. This traditional view defends the opinion that genomic resources should be public property (common good) outside trade and therefore not open to public ownership (ASSAF, 2018). The *Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes* stipulate that when research participants donate their human biological material (HBM) for research, the donor material's recipients obtain sole rights to the materials (Government of South Africa, 2012). Consequently, the law endorses the view that genomic resources should be common goods, i.e. public property, which falls outside commerce and is not open to private ownership. It gives exclusive rights to genomic resources recipients. However, the nature of the 'rights' given to recipients or users is not

explicit in the regulations. If legal rights are to be granted to genomic resources, the next question is whether it can be considered a property. The assumption can be made that lacking an unambiguous contractual agreement; the recipient would have exclusive rights in all products of the genomic resources (Thaldar, Botes and Nienaber, 2020).

One potential solution to the contradictions and uncertainties connected to rights and ownership of genomic resources is to apply to the concept of Genomic Custodianship or Genomic Sovereignty. Genomic Sovereignty can be described as representing a nation's capacity to acquire the value of its assets in the field of genomic medicine and incorporates more than the sovereign rights of states over their natural resources (Nothling-Slabbert & Pepper 2010). According to this concept, the state would take accountability for the infrastructure to manage access and use of samples and data, thereby making the samples and data the state's custodians. It will also allow donor or research participant input in what happens to their genomic resources and thereby manage exploitation, protection, sustainability, and fair access to resources (ASSAF, 2018).

Nevertheless, the notion of ownership of genomic materials is still widely debated in South Africa. As the law stands, donor participants do not seem to have ownership rights over their resources. This debate requires careful and dynamic considerations. Whether resource providers (donor participants) retain ownership or custodianship over genomic resources will have significant implications on the ethical principles of distributive justice and benefit-sharing as well as intellectual property rights in South Africa (ASSAF, 2018). It is essential to note, however, that the absence of genomic resources' rights does not imply that research participants are without rights related to their genomic resources. Donor participants can maintain a right to their genomic resources through the recipients of the resources. They could have a say on what the material will be used for, request that the material is destroyed, etc. Donor participants' rights do not have to rely on owning the resources but can be agreed upon separately (Thaldar, Botes and Nienaber, 2020).

4.3 Patents and Pharmacogenomics

Great moral significance is attached to the donation of human biological materials (HBM), resulting in vigorous discussions over the property rights and commodification of genomic resources. Existing research ethics parameters focus on autonomy principles, i.e. the participant's right to voluntarily decide what happens with their research samples by signing and informed consent to this effect. This concept is independent of any property right to one's tissue samples, and consent forms traditionally waive research participants' rights to their HBMs and accompanying benefits, which is ethically and legally challenging (Dhai, 2017).

There has been discussion and debate for some time now as to whether Intellectual Property (IP) rights such as patents can protect and commercialise IP on HMBs. Even though information obtained from genes is considered patentable in most legal jurisdictions, much debate still exists over DNA patents' basic features (Kers et al., 2014). Patents on genomic resources' discoveries may be essential to raise funding to commercially advance products (such as personalised medicine). Still, patenting can also hold back the advantages of genetic materials, specifically in low-resource countries. There is concern that patents on genes will hamper research in the public sector and escalate costs for public access to medical products and services, particularly for complicated diseases (WHO, 2005).

A patent gives the patent owner the right to exclude competitors from exploiting their inventions for a stipulated period. A patent is a certificate provided by or on behalf of the government, confirming that it meets certain requirements. The patent owner has the right to prohibit other persons from utilising or profiting from the patent without their approval and gives the inventor time to commercialise their discovery, recover their investment and make a profit (WHO, 2005; WHO, 2007; Sterckx, 2004). The patent system was developed to protect intellectual labour results and announce new and inventive information in the public domain (WHO, 2005). Patent holders' rights are limited by time (usually 20 years) and space (valid only in the Patent Office's jurisdiction, where the patent was granted). An invention must be novel, not obvious, useful and sufficiently disclosed in the application to obtain a patent (Sterckx, 2004). These prerequisites guarantee innovation by excluding patents for things already invented.

A gene patent is a sole right to a particular DNA sequence granted by a government to an individual, organisation, or corporation who asserts to have initially recognised the gene. Once an applicant is awarded a gene patent, the patent holder decides how the gene can be utilised in commerce, such as medical or scientific genetic testing, and in non-commercial environments such as research, for 20 years from the patent date. Gene patents have regularly ensued in companies having exclusive gene testing ownership for patented genes (MedilinePlus, 2020). Some argue that human biological materials (HBMs) cannot be patented because they naturally occur and do not represent an invention but rather a discovery. Others reason that technology would not have advanced if innovations, such as genetic information, had not been protected (Kers et al., 2014).

Furthermore, with the completion of the Human Genome Project in 2003, all human gene sequences were in the public domain, which means they were no longer "novel". Notwithstanding these opinions, a considerable part of the human genome has already been patented by pharmaceuticals, biotech firms, and research institutions. This introduces an additional debate on the effect of patents on genetic information and the development of medicines. Patents may constrain the use of essential genetic information and threaten biomedical research, and translate research discoveries to clinical application. Large amounts of patents associated with the human genome could constrain the incorporation of genomic medicine into healthcare due to restrictive patents and high costs (Kers et al., 2014). Diagnostics related to patented genes are a novel discovery since the actual DNA sequence to be tested, and not the technique of analysing the gene to establish its sequence, is applied for the patent. Consequently, only the patent holder or licensee has permission to sequence the DNA during the patent's existence (Cook-Deegan & Heaney, 2010).

The disputes surrounding gene patents made it to court in the USA in two notable cases. The first is *Diamond vs Chakrabarty* [447 US 303 (1980)]. The plaintiff created a novel species of a bacterium capable of metabolising hydrocarbons in naturally occurring organisms using recombinant DNA processes, which demonstrated immense potential in the handling of oil spills. The plaintiff submitted

an application for a patent denied by the defendant (patent office) because the microorganisms were products of nature and unpatentable. The court held that although a naturally occurring product may not be patented, a genetically engineered microorganism is not naturally occurring and may consequently be patented. In the case of *Association for Molecular Pathology vs Myriad Genetics Inc.*, [569 US 576 (2013)], the validity and constitutionality of the BRCA1 and BRCA2 gene patents on which Myriad Genetics had been applying for their exclusive license against other laboratories and researchers, were contested. Opponents of Myriad focussed on the excessive price of tests and the subsequent health inequality between those with the means to be treated and those without didn't. Judge Sweet ruled the information coded in the gene, not just the molecular composition, makes the gene valuable to the patent holder. Since the unprocessed data coded in the gene is a natural origin product, it is not patentable. On appeal, the court upheld part of Judge Sweet's decision. Still, it overruled the argument about the information content by concentrating on the fact that isolating a gene interrupts the bond between the molecules within the DNA, in that way producing a new substance. The plaintiffs appealed this decision to the Supreme Court, and on June 13, 2013, the court unanimously found that isolated but unchanged genes were natural products and therefore unpatentable. The court further ruled that synthetic DNA molecules that include only exons (part) of a gene require an innovative phase and consequently remains patent-eligible (Cook-Deegan & Heaney, 2010; Savers, 2013).

Most PGx tests in health research rely on a small number of Single Nucleotide Polymorphisms (SNPs) to pinpoint genetic alternatives related to treatment response. Individual SNPs are products from a natural origin. Therefore, they are not patentable, but when a direct link can be shown between the SNP and the phenotypic response, patent applications will be concentrated on claims related to SNPs' utilisation rather than the SNPs themselves.

PGx related patents will typically involve three types of claims:

(i) Those related to methods of testing which will be responsible for identifying patients who may have a specific genetic response to treatment;

(ii) Those pertaining to methods of treatment including the dispensing of medicines to patients with a particular phenotype response;

(iii) Those related to novel dosages of medications that will stipulate the suitable dosage for patients with specific genetic variants (Nuffield Council, 2003).

How inventors claim their rights of proprietorship of PGx developments through patents will directly impact research and development and the dissemination of pharmacogenomics-based treatment and information. Thus, if patents limit healthcare access due to additional costs and inconvenience on research and development, it may prevent research into new medical treatment. This can be particularly detrimental to low-resource countries. One of PGx research benefits, namely decreased time and costs of clinical trials, may consequently be invalidated (WHO, 2007).

In the case of existing medicines, the potential benefits of PGx have already been demonstrated with the use of enzymes, such as the CYP-enzyme, where genetic variations may result in differential metabolism of existing HIV treatments. However, it is not clear who would conduct PGx analysis on existing medicines to extend patents. If a medicine is still under patent, pharmaceutical companies may be inspired to conduct PGx research to extend their patent. Still, once a patent no longer protects the medication, there will be no financial benefits for the company to enhance its use (Nuffield Council, 2003; WHO, 2005). Granting patents for PGx research discoveries can be considered an essential means of encouraging new inventions and progress. Still, it is vital that in awarding these patents to the inventors, the patents do not impede the public's right to access life-saving medicines (Nuffield Council, 2003; WHO, 2007).

4.3.1 The Role of Patents in PGx Research in South Africa

Due to South Africa's high incidence of communicable and non-communicable diseases, heavy reliance is placed on locally produced or imported medicines of which most are patented. Patented medicines are costly because pharmaceutical companies want to recover the costs related to the research, development, and production, which means that underprivileged communities can often not afford essential treatments (Ndlovu,2014).

Patents related to PGx developments in South Africa are protected under South Africa's Patents Act No. 57 of 1978. The Act regulates many facets of inventions that have a direct influence on access to medicines. In terms of Section 25(1) of the Act, "A patent may, subject to the provisions of this section, be granted for any invention that involves an inventive step and which is capable of being used or applied in trade or industry or agriculture" (Act 57 of 1978). Parallel to the patent holder or licensee's proprietary right is South African communities' right to access affordable healthcare, which is included in The Constitution of the Republic of South Africa (Act 108 of 1996) (Ndlovu, 2014).

As a member of the World Trade Organisation (WTO), South Africa is a signatory to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), adopted by the WTO Morocco on 15 April 1994. The TRIPS agreement allows member states to pass Intellectual Property (IP) legislation, including patent laws, so that the IP rights do not hinder legitimate business but ensures that “technology is transferred and disseminated in a manner conducive to social and economic welfare”. This allows member states scope to establish laws in the perspective of their socio-economic and other unique circumstances by providing for some flexibility (WTO, 1994).

As a member of the African Union, South Africa is a party to the African Commission on Human Peoples Rights' 2008 resolution on access to medicines. This resolution acknowledges that “access to needed medicines is a fundamental component of the human right to health” and urges member states to refrain from executing IP policies that do not take advantage of the TRIPS Agreement's flexibilities (African Commission, 2008). Regardless of the resolution's stipulations, the South African Patents Act still has weaknesses that are considered a contributing factor to the high prices of medicine in South Africa. For example, the Act allows for patenting new uses of known substances, which is likely to encourage “ever green” patents whereby “new inventions” are just small changes to existing medicine patents. Usually, evergreening does not involve looking at any meaningful therapeutic improvement but instead looking at a company's economic benefit (Collier, 2013). Evergreening can prevent the entry of generics into the market and avoid the access

of medicines where genetic variations may result in differential treatment. The TRIPS Agreement does reference patenting of new uses of know substances.

The South African government recognised the above-mentioned weakness in the South African Patent Act, which led to the *Draft National Policy on Intellectual Property* (2013). This policy was published by the Department of Trade and Industry's consumer and corporate regulation division and recognises a direct connection between patent protection in South Africa and the high costs of medicines in South Africa (DTI, 2013). It further acknowledges South Africa's disease burden and realises that it may benefit from the TRIPS Agreement's flexibilities as a member of the WTO. Specifically, adopting a procedure that would warrant that only new processes and products whose manufacturing includes an innovative step are granted patent status is a deliberate effort to accommodate public health matters (Ndlovu, 2014). Chapter 2 of the policy recognises that the Intellectual Property (IP) system is one of the elements that directly influences access to healthcare. There should be a balance between trade and health concerns with regard to patent protection. The policy proposed that South Africa scrutinise patent applications before awarding them and suggested higher standards when deciding whether a medicine merits a patent. It further states that where local or indigenous information (such as genetic information) is used in developing patents, provision should be made to disclose the origin of the genetic resources/information. Furthermore, prior informed consent from those providing the resources and benefit-sharing agreements or co-ownership of patents must be obtained, where applicable (DTI, 2013).

In reaction to the draft IP Policy publication, the Mail & Guardian uncovered a pharmaceutical plot in January 2014 to undermine and delay the IP policy. The so-called PharmaGate scheme proposed that a front organisation, which seemed South African, be set up to run independent research. The research would then be sent to a public relations agency in the United States to manipulate the research's objectives to mislead policy-makers and the South African public. The plan aimed to indirectly persuade the South African government to strengthen, rather than lessen, patent protection for vital medication. Although the plan contained no suggestion of rudimentary efforts to obtain influence openly, it resulted in a call to the Department

of Trade and Industry to finalise the IP Policy (De Wet, 2014). In 2018, the first phase of the IP Policy in South Africa was approved. Phase 1 focuses on IP and public health and international IP cooperation. Concerning public health, the policy recognises no connection between an escalation in IP protection and innovation. However, it identifies a need for a more robust framework to ensure objectives, such as public health, are met . The IP Policy is considered the first phase towards an all-inclusive IP policy and positive development in the efforts taken by South Africa to include TRIPS flexibilities into an amended Patents Act. It is hoped that once the law has been amended to include these flexibilities, access to life-saving medicine will no longer be a concern. It will exclude the unreasonable promotion of multinational trade interests that sacrifice all South Africans' health and well-being (Ndlovu, 2014). When genomic resources are used to generate benefits, such as intellectual property rights (patents) in personalised medicine, the benefit should be allocated appropriately. Benefits should not be limited to the entity that innovated the patent but should reach the community whose genetic resources were used to generate the intellectual property (ASSAF, 2018).

4.4 Conclusion

Irrespective of the national and international attempts to characterise genomic resource ownership, it is still unclear who owns genomic resources and who is entitled to the resources' economic benefit. PGx research can be of great benefit to healthcare with the introduction of personalised medicine. However, for these benefits to be realised, comprehensive legislation and guidelines are needed to ensure PGx treatments are affordable in public health while still offering protection of inventors' intellectual property rights. Local and international sources provide a strong foundation for setting up such guidelines and should be incorporated into a workable solution for all.

CHAPTER 5: SOCIAL IMPLICATIONS OF PHARMACOGENOMICS RESEARCH IN SOUTH AFRICA

5.1 Introduction

Fears exist that Pharmacogenomics (PGx) development will intensify prevailing global health inequalities. Aspects that will play a role in the equitable growth and integration of PGx include financial limitations and barriers to PGx implementation, social discrimination, and stigmatisation based on genetic considerations and ethnicity or re-emergence of racial characterisation. In countries or regions with existing burdens on healthcare systems, PGx must be proven to be economically viable, effective and limit the risks of stigmatisation before implementation. This chapter explores both the socio-economic as well as social implications that PGx may have on communities.

5.2 Socio-Economic Factors of Pharmacogenomics in Research

It is expected that PGx research may result in cost-effective treatments as it uses genomic information to improve treatment effectiveness and reduce toxicity. However, to demonstrate the economic benefits of PGx research, it first requires that pharmacogenomic testing show evidence of clinical effectiveness. This can only be achieved by increased comparative efficacy research and added prominence on including costs in the decision of the significance of pharmacogenomic testing to health care (Devarka et al., 2010)

5.2.1 Financial Limitations and Barriers to Pharmacogenomics Implementation

The time needed to develop a new pharmaceutical is approximately 12 to 15 years at the cost of more than $500 million. Statistics show that only one in every 10,000 molecules synthesised results in a marketed medicine. Consequently, PGx may benefit health care by reducing pharmaceuticals' research and developmental costs from an economic perspective. This will result in the development of medicines explicitly suited for those most likely to benefit by predicting efficacy, the likelihood of adverse reactions, and the pharmacokinetics and pharmacodynamic effects. It is estimated that PGx could save up to 45% of pharmaceutical development costs, which should effectively make pharmaceuticals cheaper (Reeder & Dickson, 2003).

Conversely, PGx treatment may be more costly than existing medicines, as it may effectively exclude adverse responders and non-responders from the market of certain pharmaceuticals, resulting in reduced markets, reduced production, and potential price increases (Reeder & Dickson, 2003). Suppose PGx research participants in low-resource countries are unable to afford personalised medicine. In that case, they will also not enjoy its benefits, thereby limiting improvements in the care they receive. Furthermore, the medical problems that bring about the highest morbidity and mortality in low-resource countries are relatively rare in the developed world. Consequently, if personalised medicines are effective in these countries, research efforts will have to be expanded to include work on the medical conditions prevalent in them (Brothers & Rothstein, 2015).

Added costs related to PGx-based medicines are the costs of genetic screening and analysis. To personalise medicine, each individual will have to be genotyped, which necessitates infrastructure, technology, investigations, counselling, training, and oversight. It will require pharmaceutical companies to market the medicines in conjunction with genetic tests for results and safety. Countless individuals in low-resource countries will not be able to afford genetic testing. Unless genetic testing is provided free of charge or subsidised, no action will be taken regarding PGx testing and prescribing (WHO, 2007). Advocates for personalised medicine have claimed that genetic tests might enhance health by helping people recognise health risks and embark on health behaviour changes that could minimise these risks. However, the probability that this information will help individual patients make significant changes in health behaviours will be substantially influenced by their financial resources or the particular country's healthcare system (Brothers & Rothstein, 2015).

Hand-in-hand with genetic testing is counselling and counsellors to assist research participants, patients, and healthcare providers in interpreting and understanding results. An increased need for genetic screening- and diagnostic testing will result in a substantial escalation in health care expenses before PGx-based research or treatment. Increased costs will cause an additional economic load on healthcare systems and have a considerable impact on the affordability of personalised medicines in low-resource countries (Reeder & Dickson, 2003). Furthermore, PGx research may emphasise clinical trials conducted on participants expected to

respond well to the treatment. This will result in smaller or less genotypically varied trial groups, a more significant risk of adverse events going undetected, and a potential decrease in the safety of the treatment's market application. In developing countries that do not have the infrastructure for efficient and trustworthy genetic testing, these treatments may become perilous, especially if they were designed to be used together with genetic tests. Furthermore, if the market dictates the participants' selection process in clinical trials, the marketing/registration license span may be more restricted and exclude certain genetic groups (WHO, 2007).

Pharmacogenomic medicine can reduce Adverse Drug Reactions (ADRs), which places an enormous burden on healthcare systems. Also, the unsuccessful use of pharmaceuticals places excessive demand on healthcare resources. Consequently, pharmacogenomic medicine may have a positive economic effect on healthcare systems. However, since PGx treatment will, in all likelihood, be more expensive than conventional treatments, it will need large-scale financing in the healthcare infrastructure. Furthermore, with genetic testing comes the costs of genetic screening, analysis, counselling, and pharmacovigilance. Increased costs will put additional strain on the healthcare infrastructure and may be economically too challenging to bring PGx to realisation in low-resource countries (WHO, 2007). This will result in the unintentional widening of healthcare affordability inequalities between the wealthy and the under-resourced. In low-resource settings, health systems may also consider progressive genomics technology secondary to the delivery of primary, vital healthcare.

Healthcare systems in low-resource countries urgently need more emphasis on the potential outcome of pharmacogenomic discoveries, which can be translated into feasible solutions in the healthcare setting. Convincing low-resource health systems to make the required changes must originate from an evidence-based approach that meticulously questions whether a genetic test and PGx medicine legitimately improve quality of care in a cost-effective way. This will have to happen before health authorities can be persuaded to implement PGx medicine in their health systems (Kapoor et al., 2016).

5.3 Social Implication of Pharmacogenomics (PGx) research

Irrespective of the potential benefits to civilisation made possible by PGx research; complex social concerns arise embedded in privacy and confidentiality and the disclosure of genetic information. The exposure and use of genetic information may have several social implications for individuals or groups, including uncovering unexpected information, discrimination, and stigmatisation (ASSAF, 2018).

5.3.1 Incidental findings

One of the social challenges of genomic practice, whether for research or in clinical practice, is the probability of discovering unforeseen and un-called for findings, so-called ‘incidental findings’. Incidental findings can be highly upsetting and may cause psychological distress to patients and research participants. Conversely, incidental findings may give patients and participants the power to embark on changes that avert or postpones disease (ASSAF, 2018). Genetic testing for PGx research or clinical practice introduces the concern for ethical practice in a science where the borders of what is pursued and what can be known is distorted. Genetic testing can be perceived as both a choice and a responsibility which indicates a conflict between autonomy and the moral imperatives of choice and responsibility. Conflict arises due to the possibility that genetic tests can also reveal mutations of genetically transmitted diseases. This makes the patients or research participant the owner of information related to risks for a condition to which his/her relatives with the same genetic mutation may be exposed (Cowley, 2016).

Before genetic testing is conducted on patients or participants, they must be informed of the potential incidental findings and given the option about whether they wish to be informed and, if so, which results they want to be informed about. This information should be included in the consent process while obtaining consent to do genetic testing. Furthermore, researchers and clinicians should explain what will happen in the event of incidental findings. Patients and participants have a right not to know of any unexpected results, therefore the importance of genetic counselling before testing. The choice to inform relatives of incidental findings and the possible propensity to certain diseases remains the patient's decision or participant. The clinician and the researcher should endeavour to educate the patient on the significance of genetic information to his/her relatives. However, if the patient

decides not to tell family, non-consensual sharing of this information is prohibited. Yet, in the circumstances where the risk of an intra-familial genetic disease is great, and the patient's relatives have an opportunity for prevention or early intervention, the sharing of information may be pertinent. It is possible to disclose confidential information about a research participant without their consent if there is a significant risk to others. The HPCSA guidelines state that the risk of harm must be severe enough to outweigh the participant's right to confidentiality. An effort must always be made first to obtain the participant's consent, but disclose, however, if consent is not forthcoming (HPCSA,2008). Still, the risk of sharing the likelihood of genetic disease may lead to discrimination by insurers and employees. It may also lead to psychological implications by adversely influencing self-image; patients may be confronted not only with the weight of suffering from a stigmatised condition but may also be told that they cannot be treated effectively (Butnariu, 2015).

With specific reference to clinical trials, there is no agreement at present if individual results from research, including genetic tests, should be provided to participants or by what means it should be done. Many researchers contend that participants should not be given information directly connected to their genetic make-up. The consensus is that the decision to provide incidental findings should be established by the participant's desire to be informed, the research design, and the clinical value and vigour of the produced information (Morley & Hall, 2003). The CIOMS guidelines propose that specific genetic research findings be returned to donors if requested if the following guiding principles for return of results are followed: results must have analytical validity, clinical significance, and actionability to qualify for being returned. This infers that life-saving information and data of direct clinical use involving a substantial health concern must be presented for disclosure. Information on undecided scientific value or clinical importance would not qualify for revelation to the participant (CIOMS, 2016).

5.3.2 Discrimination, Stigmatisation and Stratification

Physical risks related to PGx research are uncommon. However, social risks are often associated with this type of study and can extend beyond the individual participant to population groups that the participant is linked to. Social harms include

discrimination and stigmatisation, resulting in population or disease stratification (Dhai, 2017).

Discrimination can be defined as a legally or socially unacceptable division between individuals, mostly based on stereotypes instead of assessing individual value, capability, or worth (Brothers & Rothstein, 2015). It results in society's intolerable stratification and denial of vital opportunities to members of a specific group or population. Discrimination can also result in distinctions between people in ways that are considered socially acceptable within a particular context. For example, in the insurance industry, it is acceptable to treat specific individuals differently based on their risk profile. There is a sound actuarial reason for doing so. Genetic discrimination is exhibited when people or patients are mistreated because of differences in their DNA. Genotype-based discrimination is a significant concern introduced by academics examining the ethical, legal and, social implications of the Human Genome Project. This view is based on the belief that individuals will be hesitant to undergo genetic testing, regardless of the potential health benefits, if it could result in discrimination. PGx research could contribute to genetic discrimination. It may show that participants are more prone to develop a specific illness or condition in the future or indicate that participants would not react to standard treatment, thus signifying increased morbidity and mortality risk (Bothers & Rothstein, 2015).

Genetic discrimination has become the focal point of human rights protection by adding detailed provisions in international declarations. In terms of Article 7 of the UNESCO *International Declaration on Human Genetic Data*: “(a) Every effort should be made to ensure that human genetic data and human proteomic data are not used for purposes that discriminated in any way that is intended to infringe, or has the effect of infringing human rights, fundamental freedoms or human dignity of an individual or for purposes that lead to the stigmatisation of an individual, a family, a group or communities.
(b) In this regard, appropriate attention should be paid to the findings of population-based genetic studies and behavioural genetic studies and their interpretations” (UNESCO, 2003).

In South African Law, the right to equality and equal protection is affirmed in section 9 of the Bill of Rights (South African Constitution) which provides that 'neither state nor any person may (directly or indirectly) discriminate unfairly against anyone on any one or more grounds, which include race, gender, sex, pregnancy, marital status, ethnic or social origin, colour, sexual orientation, age, disability, religion, conscience, belief, culture language, and birth'. A person's health status, which might incorporate a diagnosis or a tendency to a genetic disorder, is not mentioned in section 9. It may, however, be integrated under "disability". In *Hoffman v South African Airways* (2000) the right to equality, based on HIV-positive status, was considered. The Constitutional Court maintained HIV was not a "disability" but did find that discrimination on the grounds of HIV status would violate dignity as it was discrimination based on a person's health. Similarly, unjust discrimination on the grounds of a person's genetic make-up would be unconstitutional.

Further concerns have been raised about the possible effects of genomic research on population groups, specifically concerning stigmatisation harm. Stigmatisation is connected to discrimination and is most likely the reason and consequence of unfair discrimination (ASSAF, 2018). Genomic research can lead to the distinct linking of disease to particular races or ethnic groups that may be utilised to promote animosity or to affirm the social and cultural upper hand of one ethnic group. Stigmatisation is considered a reason for low self-esteem, social rejection, mockery, and isolation. A further concern is that genomics data could be applied to make normative statements regarding people with diverse ethnicities or races. An example used by De Vries et al. mentions a well-known geneticist who conveyed an opinion that genetic research may lead to the discovery of genetic factors rationalising variation in the 'power to reason' between Africans and Westerners (De Vries et al., 2012).

If detrimental polymorphisms (one of two or more variants on a DNA sequence) are more frequently connected with particular ethnic groups, members of that group could suffer stigmatisation. Including genotypically related groups in clinical trials could also strengthen social marginalisation. The use of racial or ethnic classification in PGx research may result in using these categories in the analysis of study results, marketing, and prescription of medicines. Consequently, participants from certain ethnic groups may be refused access to specific treatments. For example, research

indicated that a particular treatment for heart disease was less effective for African Americans. Based on these results, some clinicians refrained from prescribing the medicines to African American patients, although some may have benefitted (Morley & Hall, 2003). However, race and ethnicity do not equal genotype, and there can still be vast genetic differences among the various racial and ethnic groups. To incorrectly label specific races or ethnic groups as more likely to have certain diseases or react in a specific way to certain medicines runs the risk of incorrectly stigmatising members of those racial or ethnic populations. This may rejuvenate the concept of biological differences that have brought about racially unequal healthcare (Peterson-Iyer, 2008).

The disparity between racial and ethnic groups causes extensive debate about the meaningfulness of racial classification in genetics. There are two contradictory arguments concerning pharmacogenomics and race. The first advocates that some ethnic or racially identified populations have a positive response to particular medication due to biological differences, which may add to health inequality. The second group argues that race will be superseded once fundamental variations are identified. However, genetic diversity studies that aim to classify people according to race are harmful due to discrimination and stigmatisation and environmental contributions to diseases continue to be ignored (WHO, 2007).

A recent example of research where research participants were classified according to race is the controversial study on women of colour conducted by the University of Stellenbosch. According to this study, which has been severely criticised, women of colour have an increased risk of low cognitive functioning due to low education and unhealthy lifestyles. A group of academics called for the publication's subtraction, saying the research had “racist ideological underpinnings, flawed methodology, and its reproduction of harmful stereotypes of ‘coloured’ women” (Pretorius, 2019). While this research is not genetic, it provides ample evidence of the potential problems resulting from research attempting to classify participants according to race.

The inclusion of population groups in PGx health research is that results may add to current stigma for the population groups, specifically where the research includes stigmatised conditions or where the groups are at present socially and economically

relegated. To this effect, the following general best practice guidelines can be followed:

i. Researchers must take additional precautions not to publish research results that could be seen as stigmatising by the groups or others.
ii. Where PGx research is conducted on groups that are specifically vulnerable, researchers must carry out wide-spread community engagement to assure the groups comprehend and support the research, understand the nature and effect of existing stigma.
iii. There should be occasion for researchers and groups to agree on a suitable way describe research results (ASSAF, 2018).

Stratification involves the arrangement or classification of people or objects into different groups. For PGx research purposes, a distinction can be made between patient/population stratification and disease stratification. Patient or population stratification can be defined as the classification of groups of patients following genetic markers related to a risk of an adverse reaction to medication or a favourable response to medication. Disease stratification is the procedure by which diseases are sub-classified per genetic measures. It presents the possibility to advance the diagnosis and, therefore, treat disease (WHO, 2007).

Patient or population stratification may offer more efficient prescribing of medication. Still, it may also present patients with fewer treatment options if they do not respond adversely to medication. Population stratification may result in sub-groups of populations who are too insignificant to promote research and development in that specific subgroup, resulting in their exclusion from clinical trials. These groups may be confronted with a situation where they have minimal treatment alternatives available to them or be left without any effective treatment (Morley & Hall, 2003).

Disease stratification involves the classification of groups of patients related to genetic markers associated with either a risk of an adverse response or a favourable response to therapy. The potential benefits of disease stratification would be to assist in the choice of treatment and improve diagnosis. However, disease stratification brings about various concerns. Firstly, it can create novel genetically stratified groups that may lead to genetically based discrimination and present new

ethical concerns related to equity in health. These include screening out certain genetic groups during the development of new medicines and creating unknown risks that will be unevenly shared between genetically defined groups. It may also lead to withholding treatment, stigmatisation, and social discrimination due to a person's categorisation in a specific genetic group. Secondly, pharmacogenetics can interact with prevailing social stratification by reserving expensive personalised medicine for the wealthy (Smart et al., 2004). If diseases are further stratified into sub-categories in line with genetic standards, illnesses that are difficult to treat or do not react to available treatment may be left untreated. The same applies to prevailing conditions in developing countries, as fewer medicines are created for those diseases (WHO, 2007).

However, it is essential to note that it is not always morally incorrect to treat people differently. Different patients may require different treatments, and treating all patients the same in these instances can be considered immoral. For example, suppose a specific medication is effective in patient A but causes severe adverse drug reactions in patient B. In that case, there is an ethical obligation to avoid using the medicine in patient B. Pharmacogenomics and personalised medicine has the potential to utilise a patient's association with a genetic group to avoid ADRs, to focus on effective treatment dosages, and select appropriate alternative treatments, where indicated. This will allow healthcare to be supplied in a more efficient, ethical, and morally significant way. Furthermore, PGX may connect positively with general classifications of variations between patients. If the genetic foundation for a response to treatment appears to socially characterise ethnic or racial populations, it could assist in effective and ethical healthcare on the condition that it is used sensitively and fittingly (Smart et al., 2004).

Advances in genomic research can further benefit public health programs in low-and-middle-income countries by separating individuals into sub-populations who differ in disease predisposition and response to treatment by dispensing the correct treatment to a vulnerable population at the appropriate time. These advances may bring about a paradigm shift from reactive medicine to proactive medicine. In this context, precision medicine can also contribute to the South African sustainable development goal 3.8 to achieve universal health coverage, including access to safe,

effective, quality, and affordable essential medicines and vaccines for all (UNDP, 2019)

5.4 Conclusion

Pharmacogenomics research and medicines are likely to have a significant impact on the treatment of diseases. However, if it is accepted and utilised in low-resource countries, efforts must be expanded to consider the economic and social barriers to implementation. Specific attention must be given to diseases prevalent in low-resource countries and the financial infrastructure needed to realise implementation. Furthermore, the implications of incidental findings must be considered, and the significance of such results must be shared with patients and research participants. Lastly, researchers and clinicians must strive to prevent unfair discrimination and stigmatisation due to population or disease stratification as a result of genetic testing.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS FOR ETHICS GUIDELINES FOR PHARMACOGENOMICS RESEARCH IN SOUTH AFRICA

6.1 Introduction

As specified in section 3.4.2 of this report, genetic sampling poses a negligible physical risk. Nevertheless, there is the risk that research participants will not be treated justly and equitably and that those who provide genetic information for research and development will not receive an adequate benefit for their contribution. Furthermore, PGx research may pose social and psychosocial risks, which may even impact groups or societies. These risks include ethnic or racial stigmatisation and disease stratification, concerns regarding genuinely informed consent, and a breach of participant confidentiality (Shaw, 2020).

Provision must be made for Ethics Guidelines for Pharmacogenomic Health Research in South Africa (PGx Ethics Guidelines), which incorporate suggestions on avoiding these potential risks while ensuring that participants and communities receive the maximum reward. This chapter aims to provide recommendations and suggestions to address some of the potential ethical and social risks of pharmacogenomics (PGx) with specific consideration to access, benefit-sharing, informed consent, and privacy/confidentiality. Reference will be made to preceding chapters to prevent unnecessary duplication of information, where applicable.

6.2 Access

"Access" within the context of PGx research can be defined as 'acquiring samples of human biological materials, including genetic materials, within a country's border, with the aim of research, commercial or industrial use'. It must not be confused with access to PGx research benefits, which falls under the ambit of benefit sharing.

As indicated in section 3.4.3.1 of this report, the Nagoya protocol provides a solid foundation for better legal confidence and clarity for providers and recipients of genetic resources. It expects countries to create laws to guarantee that the utilisation of genetic resources is performed with preceding informed consent (PIC) and mutually agreed on terms (MAT) (CBD Secretariat, 2011). In line with the Nagoya protocol requirements, the South Africa Minister of Health published a standard

material transfer agreement (MTA) in the Government Gazette (4171 of 20 July 2018) (Appendix 1). The MTA stipulates that South African research establishments contributing human biological material for health research or clinical trials must have an MTA in place based on the published MTA template.

However, the MTA's published version provides minimum content and principles for MTAs that fall under its application. The SA MTA sets out a 'framework', which implies that the MTA terms do not have to be copied word for word, but it is not clear to what extent parties can deviate from the template. The content and principles can be clarified and expanded through amendments by the South African Minister of Health; however, this will require stakeholder engagement and may be a lengthy process. PGx Ethics Guidelines can guide the MTA's ambiguities and provide interim direction in the absence of unified legislation, regulations, and guidelines. Information/Guidelines on the following is proposed:

- Precise definitions of terminology such as 'provider', 'recipient', and 'prior informed consent' required before obtaining access to genetic materials.
- The extent to which parties are allowed to deviate from the MTA template.
- Does 'biological material' include human biological material and associated data?
- Do HRECs have the legal right to be parties to the MTA, and to what extent should they execute an oversight function concerning MTAs?
- Explain how broad research participant consent must be and whether single consent can be obtained for different research projects.
- Define and explain the ownership of human biological material
- Provide constructive guidance concerning legally- and ethically-acceptable content of benefit-sharing agreements.
- Provide practical guidance concerning Intellectual Property (Thaldar, Botes and Nienaber, 2020).

6.3 Benefit Sharing

Discoveries from PGx research may not necessarily result in direct pharmacological benefit for the individuals, communities, or populations on whom the research was conducted (Wertz, 2011). However, benefit sharing demands that the manner in which PGx research benefits are shared is fair and equitable (Thaldar, Botes and

Nienaber, 2020). To ensure that participants or communities benefit from PGx research, benefit-sharing should move from local or individual benefit to a broader population-based benefit (WHO, 2007).

Benefits emerging from PGx can be material (financial or other concrete benefits) or different varieties such as capacity building, healthcare, or knowledge sharing. Benefits are not equal to gain in the financial or economic sense. It depends on the requirements, values, priorities, and cultural anticipations of communities (ASSAF, 2018). PGx Ethics Guidelines should guide how benefits may be shared between communities or societies. The following is recommended:

- Health Research Ethics Committees (HRECs) must approve a benefit-sharing proposal when reviewing health research proposals.
- HRECs must consider that benefit-sharing agreements may be complex and challenging and encourage governments, communities, and researchers in benefit-sharing proposals.
- The benefit-sharing proposals should be put together so that the degree of benefits accumulated from research participation corresponds with considerations such as the nature of the research, the research sponsor, and the research purpose.
- Guidelines must provide a minimum standard of benefits.

In the absence of legal promulgation, access to national PGx Ethics Guidelines may merit acceptance of international researchers' local requirements (Dauda & Diederickx, 2013).

In reviewing benefit-sharing proposals, HREC's must consider the following as potential population-based benefits:

1) <u>Capacity development of PGx in South Africa:</u> PGx research conducted on South African populations must be published with South African researchers and co-authors' acknowledgement. Furthermore, sponsors and researchers should develop infrastructure and programs in South Africa that are aimed at PGx phenotype analysis and genome characterisation. This will ascertain more biobanks/biorepositories' set-up to encourage PGx research and build local laboratories' capacities (Dandara et al., 2019).

2) Education/training support: PGx is by no means a novel science and has experienced drastic growth since the completion of the Human Genome Project. However, there seems to be a void between the researchers and the people who will ultimately be prescribing and using genetic medicine. For the basic science to be converted into clinical practice, healthcare professionals, regulatory authorities, research ethics committees, research participants, and communities will have to be educated about PGx. Education should include the technology, justifications, uses, and limitation behind PGx, and the ethical, legal, and social issues surrounding it.

Traditionally, the preconceived notion exists that genetic information is either entirely accurate and precise or downright immoral and evil. These perceptions must be opposed with education programs for researchers and healthcare professionals who will be responsible for including PGx into health research and the populations or individuals on who PGx research will be conducted or who will be given PGx based medicine (WHO, 2007). Information provided to researchers, healthcare professionals, and participants will have to be reliable and easily accessible. It will have to be provided so that participants can comprehend the information and its importance (Nuffield Council, 2003). Furthermore, education should not be limited to researchers, healthcare professionals, and participants but should be extended to the public as a whole and include general information about genetics and genetic testing and then expand to include information about PGx. Education programs should make people aware that PGx tests are probabilistic and not definitive in that it does not ensure adequate treatment of disease.
Furthermore, education programs should include different regions, populations, and cultures and ensure that participants have the opportunity to reveal their opinions about genetics. Merely making information available is not adequate. Participants need to understand the information and its importance (WHO, 2007).

Article 24 of the UNESCO International Declaration on Human Genetic Data reads as follows: "To promote the principles set out in this Declaration, States should endeavour to foster all forms of ethics education and training at all levels as well as to encourage information and knowledge dissemination programs about human genetics data. These measures should aim at specific audiences, in particular researchers and members of ethics committees, or be addressed to the public at

large" (UNESCO, 2003). As PGx testing is becoming a more widely used part of health research and specifically clinical trials in South Africa, there is an increasing need to educate researchers, healthcare professionals, research participants, and research communities about the nature of PGx research. Researchers have an essential role in providing research participants with the justification, purpose, and limitations relevant to PGx research. They should therefore be well educated in this regard before interacting with research participants. A lack of adequate understanding by researchers may end up doing research participants more harm than good (Nuffield Council, 2001).

The WHO *Ethical, Legal and Social Implications of Pharmacogenomics in Developing Countries* provide guidelines on the education of PGx. These guidelines are a good starting point to be included in Ethics guidelines and stipulate the following:

i) Researchers responsible for conducting PGx research should be well educated in the technological, ethical, legal, and social aspects surrounding PGx research, and consideration should be given to incorporate these aspects in medical school curricula.

ii) If PGx testing is to be conducted on a specific population, community, or ethnic group, researchers need to consult with and educate the applicable groups. The term 'genetics' and research related to genetics are often viewed with suspicion and can readily cause anxiety under research participants and communities. Educators/researchers will have to explain the complicated nature of PGx research to the communities. They will also need to explain the complexity of PGx treatment, should it become available. Community education also needs to incorporate regional variances and cultures and provide communities with the opportunities to share their views on PGx.

iii) An education program should be developed for reviewers of PGx research proposals (RECs and regulators) to introduce them to the notion of PGx research, including its proper uses and limitations (WHO, 2007).

The content of PGx training materials should be comprehensive and include as minimum information on the following:

i) The risks, benefits, and functions of genetics, genomics, and pharmacogenomics;

ii) The definition 'pharmacogenomics' and a distinction between genetics and pharmacogenetics;

iii) The type of information that will be revealed by PGx testing;

iv) The probabilistic nature of PGx must be illustrated, and it must be specified that PGx will not necessarily warrant effective treatment of disease.

v) It must be emphasised that an individual's genetic make-up is not the only factor responsible for their health status (WHO, 2007).

The responsibility for providing training on pharmacogenomics and the ethical challenges of PGx should rest with health training institutions, research sponsors, and researchers. Teaching PGx to students in health training institutions and continuously updating health professionals' knowledge will provide an opportunity to acquire knowledge and gain a better understanding of PGx. This knowledge can then be transferred to research participants and research communities. Health Research Ethics Committees can play a role in the education process by providing training on the ethics of PGx to sponsors and researchers, who can then disseminate this knowledge to research communities. It is not recommended that HRECs should reject health research applications if applicants do not provide sufficient evidence of the training and education of researchers and research participants in PGx. However, PGx training should be encouraged by HRECs, and informed consent documents and the process for informed consent for PGx research must be scrutinised for simplicity, clarity, and transparency (Kudzi et al., 2015).

6.4 Informed Consent

Consent for PGx differs from conventional clinical trials where participants can benefit from a trial medication or a comparator medication or study procedures. There may be no direct benefit for participants in a PGx study even if the research leads to future benefit for society. Samples may even be used for research not related to the initial clinical trial (Corrigan, 2005).

Due to the unconventional nature of PGx research, various concerns exist around obtaining fully informed consent from research participants as it is likely that participants feel they have to participate in the PGx component to qualify for the main clinical trial. To this effect, Ethics Guidelines for PGx research must specify that participation in a clinical trial should not be subjected to involvement in the PGx component of a clinical trial unless PGx test results are part of the clinical trial selection criteria. Where clinical trials involve a PGx element, separate informed

consent should be obtained. In this manner, all information on the PGx research is in a free-standing document to ensure participation in the clinical trial can proceed without involvement in the PGx study (CIOMS, 2005).

It must also be noted that the concept of autonomous decision making in South Africa may conflict with the concept of African communitarianism such as *Ububntu,* where collective decision-making has preference to individual autonomy or consent. Guidelines should therefore consider an alternative approach to the method of obtaining informed consent for pharmacogenomic research. Researchers must reflect on spirituality, environment and culture of research participants and realise that in terms of the African belief system, individuals exist through their community. Consideration should specifically be given to group consent that supports participants' cultural values and interpersonal relationships (Akpa-Inyang & Chima, 2021).

Furthermore, due to the scientific nature of PGx research, there is a concern that participants will not truly understand the possible implications of providing their genetic information for research purposes. To this effect, *The Declaration of Taipei* offers useful information. The Declaration addresses the collection, storage, and use of identifiable data and biological material with specific reference to Health Databases and Biobanks. It defines biological material as "a sample obtained from an individual human being, living or deceased, which can provide biological information, including genetic information, about the individual". Even though the Declaration does not explicitly address PGx research, the content of informed consent for the collections, storage, and use of biological materials suggested is appropriate for PGx research. Ethics Guidelines for PGx research should, as a minimum, incorporate these requirements (WMA, 2016):

- The purpose of the PGx research;
- The risks and burdens associated with the collection, storage, and use of the PGx samples;
- The nature of the samples to be collected;
- The procedures for return of results including secondary findings;
- The rules of access to the results;
- How privacy is protected;

- In case samples are non-identifiable the participant may not be able to know what will happen to their samples with the option of withdrawing their samples or consent;
- Where applicable, commercial use and benefit-sharing, intellectual property issues, and the samples' transfer to other institutions or third countries (WMA, 2016).

In addition to the above, research participants must be informed of their genetic information's possible uses before they consent to PGx testing (WHO, 2007). They should also be informed that once the information about their genetic make-up is acquired, they may be expected to disclose this to insurers and employees. Furthermore, participants must be aware that PGx tests may disclose information about themselves and other family members (Warnich et al., 2011).
Regarding the concerns related to informed consent for future research on human biological materials (HBMs), Ethics Guidelines for PGx research must list and explain the different types of informed consent that can be obtained for PGx research as indicated in Section 3.4.4.1 of this report.

PGx Ethics Guidelines must further provide guidance in communities where literacy and understanding of science are limited and should allow for the format or process to obtain informed consent to vary. For example, where research information is provided to participants with little or no literacy, the language used must be a language that participants understand. The participant's level of comprehension must be assessed before consent is given. The use of analogies, illustrations, and pictographs must be encouraged, and consideration should be given to providing information in different ways. The utilisation of community meetings, healthcare workers, or appropriate media can be considered (WHO, 2007).

6.5 Privacy and Confidentiality

Human genetic data is given special status as it can project genetic tendencies, influence families and communities, may hold information of which the importance is not known at the time of collection, and may have cultural implications for individuals and communities. Due to the special status given to human genetic data, attention should be given to the data's sensitivity, and appropriate measures should be put in place to protect the information (UNESCO, 2003). Sponsors, researchers, ethical, regulatory, and scientific bodies dealing with PGx in clinical trials must have an

understanding of the five categories for labelling and coding of genetic samples as specified in the FDA *Guidance Document: E15 Pharmacogenomics Definitions and Samples Coding* (2018) as defined in Section 3.4.4.2 of this report namely; Identified Samples/Data, Single-Coded Samples/Data, Double-Coded Samples/Data and Anonymised Samples/Data.

Furthermore, the following provisions of the Protection of Personal Information Act (POPIA) (4 of 2013) must be incorporated into Ethics Guidelines for PGx research:

- Genetic samples and data may only be collected if *voluntary, specific, informed consent* is provided by the research participant.
- Genetic samples and data can also be considered 'special personal information' that can be processed with *voluntary, specific consent* or if the processing is for research purposes and corresponds with s27(1)(d)(i) and (ii) conditions (POPIA).

Lastly, PGx Guidelines must clearly state that genetic markers make it possible to identify groups or communities irrespective of whether the samples are de-identified. Therefore, unspecified use of samples for genetic testing is not recommended, and a limitation should be put on the type of research conducted on these samples (Nuffield Council, 2003).

6.6 Conclusion

Pharmacogenomics (PGx) research makes it possible for scientists to concentrate on the significant aspects of a medicine's action, thereby improving the therapeutic index of treatment. It can further expedite new medications' development, resulting in smaller, safer, and more cost-effective clinical trials. By preventing medicine prescription that may produce serious side effects or have little or no clinical benefit, diseases can be treated more effectively. The addition of PGx research in pharmaceutical research conducted in Africa can improve health by providing scientific and technical knowledge that may bring down costs and reduce medicine's side effects. The African continent is not merely a large market for new medications and therapies but also an essential human genetic variation depository. Still, African researchers and populations are severely under-represented in current efforts to build capacity that can connect genetic differences to the tendency to get certain diseases and the ability to predict, diagnose, monitor, and treat diseases. South

African populations' distinctive genetic profiles bring rare challenges and exceptional opportunities for advancing and applying pharmacogenomics testing and new gene-specific treatment in South Africa. However, with PGx research comes various social, ethical, and legal challenges and the potential for South African research participants and populations' exploitation.

This report is a normative analysis of national and international literature related to ethical, social, and legal challenges in PGx research to provide a foundation for addressing these challenges. It further aims to provide background on the relevance of Pharmacogenomics research in South African populations' distinctive genetic profiles and identify the ethical, legal, and social challenges related to Pharmacogenomics research in these populations. The literature review offers valuable guidance on genetic and PGx health research implications from an international perspective. Still, it lacks insight into the unique challenges of PGx research in South Africa, such as informed consent, social and cultural differences of research populations, the exploitation of research participants, benefits sharing, access to medicine, and confidentiality.

Implementing comprehensive PGx ethics guidelines in a national ethics guidance document will guide health researchers and sponsors on PGx research challenges and potential solutions. National policies will contribute to the prospect that all parties will feel comfortable participating in PGx research in South Africa in the future. Furthermore, a review of the potential legal implications of PGx research in South Africa will build a strong foundation towards reviewing existing law to incorporate legal considerations of PGx research.
The above-suggested guidelines and recommendations are not exhaustive. They require in-depth consultation with stakeholders (health researchers, sponsors, Health Research Ethics Committees, and organisations like the Academy of Science of South Africa) before formalisation and publication. However, it is hoped that the suggestions will contribute to the fair and just treatment of participants in PGx research and support adequate benefit for their contribution.

APPENDIX I

MATERIAL TRANSFER AGREEMENT TEMPLATE - No. 41781 GOVERNMENT GAZETTE, 20 JULY 2018

MATERIAL TRANSFER AGREEMENT FOR HUMAN BIOLOGICAL MATERIALS
(hereinafter referred to as, "the Agreement ")

Entered into and between

The Providing Institution
(hereinafter referred to as, "the Provider ")

And

The Recipient Institution
(hereinafter referred to as, "the Recipient ")
And

The Human Research Ethics Committee
(hereinafter referred to as, "the HREC ")

THE PARTIES AGREE AS FOLLOWS

1. OBJECTIVE

The objective of this Agreement' is to set out a framework within which the Parties will engage in the transfer use and other processing of the Materials.

2. DEFINITIONS

2.1 Agreement:	means this Agreement and all annexures and amendments thereto
2.2 Benefit:	means, amongst others, the sharing of information; use of research results; royalties; acknowledgement of the Provider as the source of the Materials; publication rights; transfer of technology or Material and capacity building;
2.3 Benefit sharing:	means the process or act of sharing in the benefits that derive from the Project in a manner that is fair and equitable;
2.4 Biobank:	an institution or unit thereof that safeguards an organised collection of Human Biological Material and associated data from different individuals, which are usually kept for an unlimited period of time, for the purposes of health research;
2.5 Country:	means the Republic of South Africa;
2.6 Custodian:	means a person or entity entrusted by the Donor with safeguarding and protecting the Materials;
2.7 Data:	means any information, including personal information in any form derived directly or indirectly during the conduct of research or clinical care;
2.8 Donor:	means a person who has donated Materials to be used for health research purposes and / or teaching;
2.9 Human Biological Material:	means Material from a human being including but not limited to Materials Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, tissues and growth factors and any modifications or derivatives thereof;
2.10 Health Research Ethics Committee:	means a Health Research Ethics Committee which is registered with the South African National Health Research Ethics Council;
2.11 Intellectual Property:	means statutory and other proprietary rights resulting from Rights: creation of the human mind such as copyright, patents, scientific works, discoveries and trademarks;
2.12 Informed Consent:	means a formal agreement that a Donor (with legal capacity to do so) signs to give permission for donation of Materials, after being informed about the project and includes an on -going information sharing process which allows a Donor to consent to participate and determine whether and how their Materials will be utilised in the Project, as approved by the HREC from time to time;
2.13 Materials:	means Human Biological Materials and Data;

2.14 Parties:	means the Provider, the Recipient and the HREC;
2.15 Project:	means the health research project for which the Materials will be used;
2.16 Research Results:	means all products of the research, whether tangible or intangible;
2.17 Secondary Use:	means use of the Materials for health research purposes other than the uses determined in the approved protocol;
2.18 Termination Report:	means a report prepared by the Recipient and submitted to the Provider on termination of the Project.

3. AGREEMENT

3.1 The Provider hereby transfers the Materials to the Recipient, and the Recipient accepts the Materials from the Provider as fully described in Annexure A.

3.2 The Parties agree to conduct themselves hereunder in compliance with South African laws and policies, that no Materials shall be transferred for purposes of a health research project that has not been approved by an HREC.

3.3 The Provider remains custodian of the Materials; and the donor remains the owner of the material until such materials are destroyed.

3.4 Each Party undertakes to engage with the other in the utmost good faith and to conduct itself with the highest ethical standards and comply with all applicable legislation, including but not limited to, the legislative ban on the sale of or trade in tissues, gametes, blood or blood products.

3.5 This Agreement is subject to the suspensive condition that, and is of no force or effect unless and until, the HREC has approved the Project of which this Agreement forms a part and the HREC has approved this Agreement.

4. OBLIGATIONS OF THE PROVIDER

4.1 The Provider must obtain the necessary permits and authorisations for export of Materials.

4.2 The Provider shall inform the HREC and the relevant Donor(s)should the Provider be informed that the Materials have become identifiable for any reason whatsoever.

4.3 The Provider must obtain informed consent from the Donor(s), where reasonably possible and approval from the HREC, for any further uses of the Material.

5. OBLIGATIONS OF THE RECIPIENT

5.1 The Recipient may only carry out research according to the protocol approved by the HREC.

5.2 The Recipient shall protect and keep the Material confidential.

5.3 The Recipient may not transfer or otherwise provide the Material to any party, other than those parties listed in Annexure A, without approval of the HREC.

5.4 Should the Materials become identifiable for any reason whatsoever, the Recipient must inform the Provider without delay.

5.5 The Recipient shall deliver feedback to the Provider on the development and progress made with regard to the Project by supplying the Provider with updated information where relevant and in terms of applicable ethical and legal requirements.

5.6 The Recipient agrees that the Material will be located at:(entity details)

6. OBLIGATIONS OF THE HREC

6.1 The obligations of the HREC are to:
6.1.1 review and approve research proposals and protocols that require the transfer of Materials;
6.1.2 review and grant approval of this Agreement to ensure that it adequately safeguards the Material and the ethical requirements set out herein; and
6.1.3 review and approve all Secondary Use research of the Material transferred.

6.2 The HREC will be the last party to sign this Agreement and will only do so, after all the provisions set out herein, have been satisfied.

7. BENEFIT SHARING

7.1 The sharing of benefits should be discussed and negotiated between the Provider and Recipient before Materials are transferred to the Recipient.

7.2 The Parties agree to Benefit Sharing as detailed in Annexure B.

8. DURATION OF AGREEMENT

This Agreement will commence and become effective on the date it is signed by the HREC and shall continue until the Project terminates.

9. TERMINATION OF PROJECT

9.1 When the Project terminates, for any reason whatsoever, the Recipient shall provide the Provider and the HREC with a Termination Report.

9.2 The Termination Report will include, inter alia, reasons for termination, the status of the Project as at termination and the current status of the Materials.

9.3 Termination of the Project may occur under one or more of the following circumstances:
9.3.1 the Project reaches completion;
9.3.2 the Project cannot be carried out by the Recipient for the following reasons:
9.3.2.1 the Donors withdraw consent for use as contemplated hereunder and in such numbers as to render continuation of the Project impracticable or impossible;
9.3.2.2 the Recipient entity dissolves, winds -up or ceases to continue operating for any reason whatsoever;
9.3.2.3 the HREC withdraws approval for the Project in its entirety;
9.3.2.4 either Party terminates the Agreement on reasonable notice; or
9.3.2.5 a force majeure makes continuance of the Project impracticable or impossible.

9.4 The Recipient will, on termination of the project, immediately discontinue using the Material for any purpose whatsoever.

9.5 Destruction, return to the Provider, or transfer of Materials will be undertaken by the recipient, or any other arrangements made, with the express approval of the HREC.

10. INFORMED CONSENT

10.1 The Provider must obtain an informed consent from the Donor(s) to provide Materials to the Recipient to undertake the Project as contemplated.

10.2 The Provider must furnish the completed consent form from the donors together with the project protocol to the HREC for approval.

10.3 The Provider must submit the informed consent form for Secondary Uses of the Material to the HREC should the need arise for Secondary Use.

10.4 The Provider must inform the donors of developments or progress made by the Recipient in the Project and which is relevant to the Donor(s) Informed Consent.

11. DISPUTE SETTLEMENT

11.1 Should a dispute arise between the Parties in connection with this Agreement, the Parties must, within a period of fourteen (14) days after the date on which the dispute arose (the Dispute Date) meet to discuss the dispute and endeavour to resolve the dispute amicably, by mutual agreement.

11.2 If the Parties are unable to resolve the dispute in terms of 11.1 within thirty (30) days from the Dispute Date, the dispute will be referred to the senior management of the respective Parties for resolution. Senior management will use their best endeavours to resolve the dispute and their determination will be final and binding and will be carried into effect by the Parties.

11.3 If senior management of the respective Parties are unable to resolve the dispute within a period of thirty (30) days after it has been referred to them, either Party may institute action in accordance with South African laws, in a South African court, unless the Parties agree to resolve such dispute by arbitration in terms of a separate arbitration agreement.

12. INTELLECTUAL PROPERTY

Intellectual property will be dealt with through relevant laws related to the applicable protocol and underlying third party agreements, as far as there are any.

13. CONFIDENTIALITY

13.1 The Recipient shall keep the identity of the Donor(s)and the Materials secure and confidential at all times.

13.2 Confidentiality includes, but is not limited to the properties; characteristics; content;

13.3 The Provider and the Recipient shall treat all information relating to the nature and processes of the research in whatever form confidential.

14. PUBLICATIONS & PUBLICITY

14.1 Authorship of publications emanating from the use of the Materials hereunder must be in keeping with the International Committee of Medical Journal Editors Authorship Guidelines (http: / /www.icmje.org/icmie- recommendations.pdf) as amended from time to time.

14.2 Where the Recipient wishes to publish any information concerning the Project (in either oral or written form), the Provider must be notified and provided with a copy of the publication at least ten (10) days prior to submission of the proposed publication.

14.3 The Provider must inform the Recipient whether any information related to the publication must be removed or included and provide reasons to substantiate the removal or addition of such information.

14.4 The Provider must be supplied with a final copy of the publication before publication by the Recipient. The Recipient must acknowledge the Provider's contribution of the Material unless otherwise requested by the Provider.

14.5 Neither Party shall use the name of the other Party or its employees in any advertisement, press release or other publicity without prior written approval of the other Party.

14.6 Notwithstanding the above, and where relevant, publications must be subjected to the applicable protocol and relevant third-party agreements.

15. INDEMNITY

15.1 The Provider gives no warranty that the Materials are fit for the use and purpose for which they are transferred hereunder, or that they have any particular qualities or characteristics.

15.2 The Provider will not be liable to the Recipient for any claims or damages arising from the Recipient's use of the Material.

16. DOMICILIA AND NOTICES

16.1 The Provider choose as its domicilium citandi et executandi for all purposes arising from this Agreement, the addresses specified below:

Attention:

Physical:

Postal:

Telefax:

Email:

16.2 The Recipient choose as its domicilium citandi et executandi for all purposes arising from this Agreement, the addresses specified below:

Attention:

Physical:

Postal:

Telefax:

Email:

16.3 The HREC choose as its domicilium citandi et executandi for all purposes arising from this Agreement, the addresses specified below:

Attention:

Physical:

Postal:

Telefax:

Email:

16.4 Either Party may amend its domicilium citandi et executandi by means of written notice to the other Party.

16.5 Any notice, request, consent or communication made between Parties pursuant to this Agreement shall be in writing and shall be delivered by hand, or sent by prepaid registered post or by fax or email.

16.6 A notice, request, consent or communication is presumed unless the contrary is proven, to have been given:
16.6.1 if hand delivered during business hours on a business day, on the day of delivery;

16.6.2 íf posted by prepaid registered post, five (5) business days after the date of posting thereof; or

16.6.3 íf sent by email, on the first business day following the day of sending of such email.

16.7 Notwithstanding anything to the contrary contained or implied in this Agreement, a written notice or communication actually received by one of the Parties from another including by way of facsimile transmission, shall be adequate written notice or communication to such party.

17. GENERAL

17.1 This Agreement embodies the entire agreement between the Parties and no provision hereof may be altered or amended without the written mutual consent of the Parties.

17.2 Neither Party may assign or cede any benefit, obligation or interest it may have in this Agreement to any other person without the prior written consent of the other Party and the approval of the HREC.

17.3 Neither Party is regarded as having waived, or is precluded in any way from exercising any right under or arising out of this Agreement by reason of such Party having at any time extended any extension of time for, or having shown any indulgency to, the other Party with reference to any performance of any obligation under this Agreement, or having failed to enforce, or delayed in enforcing any right of action against the other Party.

17.4 This Agreement constitutes the sole record of the Agreement between the Parties in regard to the subject matter hereof and replaces any prior Agreement, which may exist between the Parties.

17.5 No Party will be bound by any representation, express or implied term, warranty, promise or the like not recorded in this Agreement.

17.6 Any amendments to this contract are of no force and effect unless reduced to writing and signed by the Parties.

17.7 No extension of time or indulgence by any Party will be deemed in any way to affect, prejudice or derogate from the rights of the Party in any respect under this Agreement nor will it in any way be regarded as a waiver of any rights hereunder or a novation of this Agreement.

17.8 The rule that an Agreement will be interpreted against the Party that drafted it shall not apply to this Agreement.

17.9 In the event of any one or more of the provisions of this Agreement being held for any reason to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability will not affect any other provision of this Agreement, and this Agreement shall be construed as if such invalid, illegal or unenforceable provision was not a part of this Agreement, and the Agreement shall be carried out as nearly as possible in accordance with its original terms and intent.

17.10 The Recipient receives only the rights as set out in this agreement and these rights are not exclusive to the Recipient.

18. AUTHORITY

Each Party signing this Agreement and on behalf of a Party hereto, hereby warrants in his or her official capacity that he or she is duly authorised by such Party to do so.

19. COUNTERPART SIGNING OF THIS AGREEMENT

19.1 The Parties agree that this Agreement may be signed at different times and in different places, and in copy provided the content of the Agreement and signatures are exact replicas (counterparts) of the originals when put together.

19.2 The signed Agreements when put together shall constitute a binding agreement between the Parties.

THUS DONE AND SIGNED on behalf of the **PARTIES** by their duly authorised representatives, in the presence of the undersigned witnesses, at the places appearing in the appropriate spaces below, on the dates as specified.

Duly authorised and on behalf of the Providing Institution

Full name:_____

Tel: _____

Designation: _____

Signature: _____

Signed at _____ on this the _____ day of 2018.

Witness 1: _____ Witness 2:_____

Duly authorised and on behalf of the Recipient Institution

Full name:_____

Tel: _____

Designation: _____

Signature: _____

Signed at _____ on this the _____ day of 2018.

Witness 1: _____ Witness 2:_____

Duly authorised and on behalf of the Human Research Ethics Committee

Full name:_____

Tel: _____

Designation: _____

Signature: _____

Signed at _____ on this the _____ day of 2018.

Witness 1: _____ Witness 2:_____

Annexure A

To be completed by the Provider and /or Recipient

The Responsible Party who will obtain the necessary permits and authorisations and arrange appropriate transport for the Material to be transferred is:

_____

Description of health research project under which the Materials will be used on transfer:

_____

Specific experimental tests that the Materials will be subjected to on transfer:

_____

Parties other than the Recipient to whom the Materials might be transferred as required by the Project:

_____

Quantity of Materials required to be transferred:

_____

Preferred method of transfer of Materials:

_____

Period within which Materials will be transferred:

_____

Frequency of exporting of Materials:

_____

Process of destruction of Materials:

_____

How confidentiality will be maintained should Materials be released into the public domain:

Annexure B

Benefit Sharing Arrangement between the Recipient and Provider

APPENDIX II

ETHICS WAIVER

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: P V Tobias Building, 2nd floor Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

Ref: W-CJ-141001-1 01/10/2014

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Marzelle Haskins.**

Project title: **Pharmacogenomic research in industry-sponsored clinical trials in South Africa: ethical, social and legal challenges..**

Reason: This study is an analysis of information in the public domain. There are no human participants

UNIVERSITY OF THE WITWATERSRAND
PROTECTION OF RIGHTS
HREC (MEDICAL)
2014 -10- 01
JOHANNESBURG

Professor Peter Cleaton-Jones

Chair: Human Research Ethics Committee (Medical)

Copy - HREC(Medical) Secretariat : Zanele Ndlovu.

APPENDIX III

TURNITIN REPORT

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ORIGINALITY REPORT

13%	11%	8%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	doi.org Internet Source	1%
2	whqlibdoc.who.int Internet Source	1%
3	hdl.handle.net Internet Source	1%
4	repository.up.ac.za Internet Source	1%
5	Submitted to University of Witwatersrand Student Paper	<1%
6	lirias.kuleuven.be Internet Source	<1%
7	Katherine I. Morley, Wayne D. Hall. "Using pharmacogenetics and pharmacogenomics in the treatment of psychiatric disorders: some ethical and economic considerations", Journal of Molecular Medicine, 2004 Publication	<1%
8	issuu.com Internet Source	

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