# Human Genetics and Genomics in South Africa:

# Ethical, Legal and Social Implications

## Consensus Study

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The Academy of Science of South Africa (ASSAf) was inaugurated in May 1996. It was formed in response to the need for an Academy of Science consonant with the dawn of democracy in South Africa: activist in its mission of using science and scholarship for the benefit of society, with a mandate encompassing all scholarly disciplines that use an open-minded and evidence-based approach to build knowledge. ASSAf thus adopted in its name the term 'science' in the singular as reflecting a common way of enquiring rather than an aggregation of different disciplines. Its Members are elected on the basis of a combination of two principal criteria, academic excellence and significant contributions to society.

The Parliament of South Africa passed the Academy of Science of South Africa Act *(No 67 of 2001)*, which came into force on 15 May 2002. This made ASSAf the only academy of science in South Africa officially recognised by government and representing the country in the international community of science academies and elsewhere.

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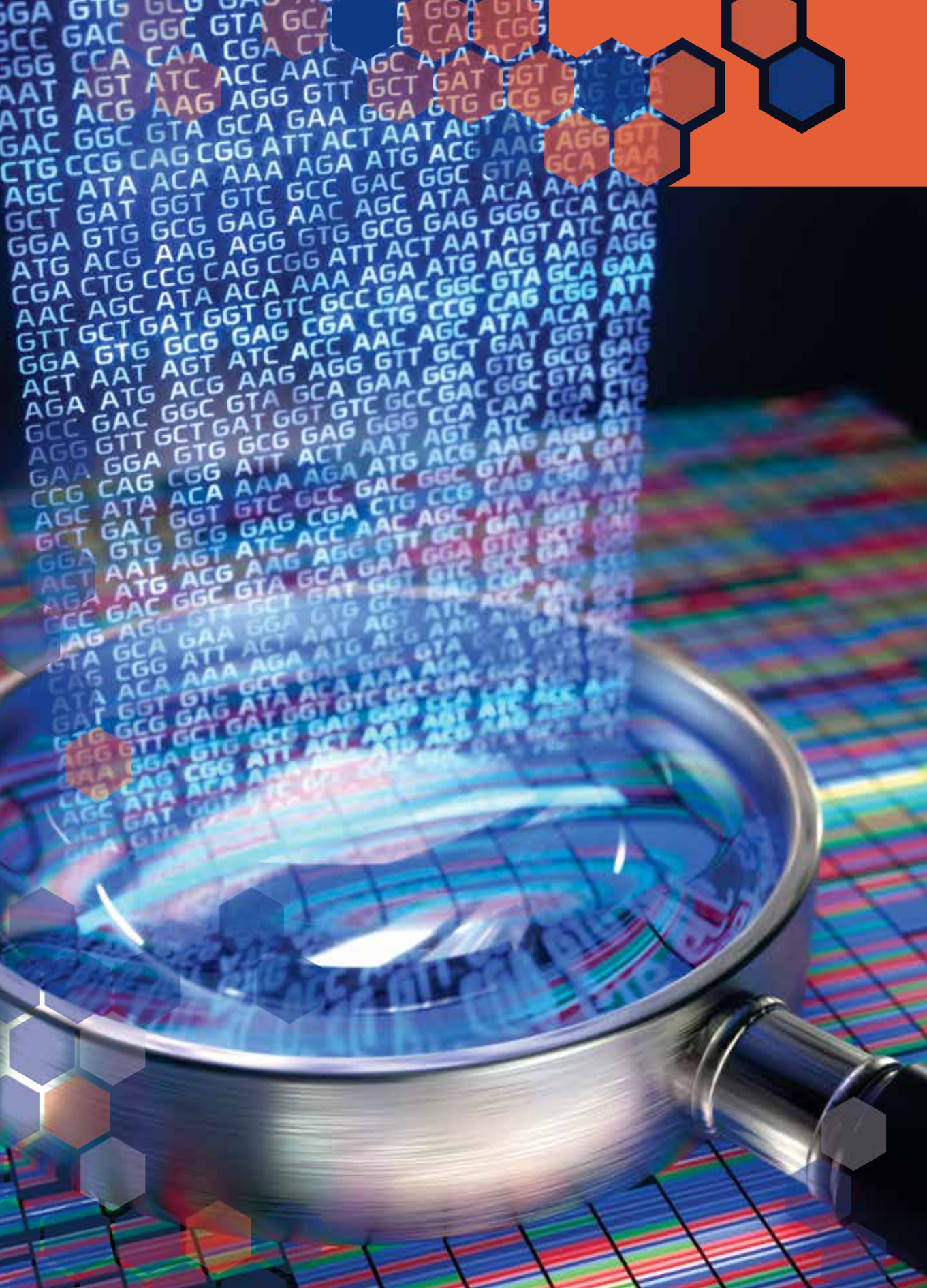


# List of Abbreviations

| | |
|---|---|
| **AFSHG** | African Society for Human Genetics |
| **AIDS** | Acquired immune deficiency syndrome |
| **ASSAf** | Academy of Science of South Africa |
| **AGMT** | African Genomic Medicine Training Initiative |
| **CAB** | Community advisory board |
| **CANSA** | Cancer Association of South Africa |
| **CBPR** | Community-based Participatory Research |
| **CGR** | Centre for Genome Research |
| **CIOMS** | Council for International Organisations of Medical Sciences |
| **COHRED** | Council on Health Research for Development |
| **DBE** | Department of Basic Education |
| **DHET** | Department of Higher Education and Training |
| **DNA** | Deoxyribonucleic acid |
| **DoH** | Department of Health |
| **DSMB** | Data and Safety Monitoring Boards |
| **DST** | Department of Science and Technology |
| **DTAs** | Data Transfer Agreements |
| **DTC** | Direct to consumer |
| **EDCTP** | European and Developing Countries Clinical Trials Partnership |
| **ELSI** | Ethical, legal and social implications |
| **HBM** | Human biological material |
| **H3Africa** | Human Heredity and Health in Africa Consortium |
| **HIV** | Human immunodeficiency virus |
| **HPCSA** | Health Professions Council of South Africa |
| **HUGO** | Human Genome Organisation |
| **IAS** | International AIDS Society |
| **IF** | Incidental findings |
| **IP** | Intellectual property |
| **IRB** | Institutional Review Board |
| **ISBER** | International Society for Biological and Environmental Repositories |
| **ISO** | International Organisation for Standardisation |
| **LIMS** | Laboratory information management system |
| **LMICs** | Low to middle-income countries |
| **MRC** | Medical Research Council |
| **MTAs** | Material transfer agreements |
| **NACI** | National Advisory Council on Innovation |
| **NBAC** | National Biotechnology Advisory Committee |
| **NDP** | National Development Plan |
| **NFDD** | National Forensic DNA Database |
| **NHA** | National Health Act |
| **NHLS** | National Health Laboratory Service |
| **NHREC** | National Health Research Ethics Council |

| | |
|---|---|
| **NIH** | National Institutes of Health of the USA |
| **NIPMO** | National Intellectual Property Management Office |
| **NQF** | National Qualification Framework |
| **NRF** | National Research Foundation |
| **OECD** | Organisation for Economic Co-operation and Development |
| **PBMC** | Peripheral Blood Mononuclear Cells |
| **POPI** | Protection of Personal Information Act |
| **R** | Recommendation |
| **REC** | Research Ethics Committee |
| **RNA** | Ribonucleic acid |
| **SACNASP** | South African Council for Natural Scientific Professions |
| **SACORE** | Southern Africa Consortium for Research Excellence |
| **SADC** | Southern African Development Community |
| **SAMA** | South African Medical Association |
| **SANAS** | South African National Accreditation System |
| **SAHGAB** | South African Human Genetics Advisory Board |
| **SAHGP** | South African Human Genome Project |
| **SAHPRA** | South African Health Products Regulatory Authority |
| **SASHG** | Southern African Society for Human Genetics |
| **SBIMB** | Sydney Brenner Institute for Molecular Bioscience |
| **SOPs** | Standard operating procedures |
| **TYAN** | TWAS Young Affiliates Network |
| **UNAIDS** | Joint United Nations Programme on HIV/AIDS |
| **UNESCO** | United Nations Educational, Scientific and Cultural Organisation |
| **URL** | Uniform resource locator |
| **USA** | United States of America |
| **VUS** | Variants of uncertain significance |
| **WES** | Whole exome sequence |
| **WGES** | Whole genome and exome sequencing |
| **WGS** | Whole genome sequence |
| **WHO** | World Health Organisation |

# Glossary

**Biobank**

A biobank is defined as an organised collection of human biological material (HBM) and associated data from participants, often stored for an unlimited period of time, for the purpose of health research, and managed according to professional standards under a documented governance structure. This would include processes and procedures performed according to international guidelines, for example, those of the International Society for Biological and Environmental Repositories (ISBER) (www.isber. org) or equivalent. HBMs include any specimen of human origin, including tissues, body fluids and their derivatives. Typically, this would include (but is not limited to) sputum, saliva, whole blood, serum, plasma, peripheral blood mononuclear cells (PBMCs), deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, semen and cell cultures.

**Blood product**

Is any therapeutic substance prepared from human blood. This includes: whole blood; blood components (red cells, platelets, fresh frozen plasma and cryoprecipitate); and plasma derivatives.

**Community**

Refers to a small or large social unit that shares values, norms, identity, cultural or religious beliefs that gives rise to a shared understanding of what is needed for their well-being.

**Forensic medicine**

A branch of medicine dealing with the application of medical knowledge to establish facts in civil or criminal legal cases, such as an investigation into the cause and time of a suspicious death. Also known as forensic pathology.

**Forensic science**

The application of science to criminal and civil laws (mainly on the criminal side) during criminal investigation, as governed by the legal standards of admissible evidence and criminal procedure.

**Genetics**

Refers to the study of genes, genetic variation, and heredity in living organisms. It is generally considered a field of biology but intersects frequently with many other life sciences.

| | |
|---|---|
| **Genomics** | A branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes. |
| **Informed consent** | The process by which a patient/research participant learns about and understands the purpose, benefits, and potential risks of a medical, surgical intervention and research study, and then agrees to receive the treatment or participate in the study. Informed consent generally requires the patient or responsible party to sign a statement confirming that they understand the risks and benefits of the procedure, treatment or research. |
| **Stem cell** | An undifferentiated cell of a multicellular organism which is capable of giving rise to indefinitely more cells of the same type, and from which certain other kinds of cells arise by differentiation. |
| **Tissue bank** | An establishment that collects and recovers human tissue for the purposes of medical research, education, and allograft transplantation. It may also refer to a location where bio-medical tissue is stored under cryogenic conditions and is generally used in a more clinical sense. |
| **Transplantation** | The process of taking an organ or living tissue and implanting it in another part of the body or in another body. |
| **Translational research** | Is separated into four segments: T1 is the translation of basic science into clinical research (phase 1 and 2 clinical trials); T2 the further research that establishes relevance to patients (phase 3 trials); T3 is translation into clinical practice; and T4 is the movement of scientific knowledge into the public sector. |

# Foreword

The Academy of Science of South Africa (ASSAf) is mandated to provide evidence-based science advice to government on matters of critical national importance. This consensus report is in fulfilment of this mandate. Great benefit is to be derived from the work done in the fields of genetics and genomics, which has the potential to impact positively on the health and quality of life of all members of society. Work in these fields is also likely to impact positively on the economy through job creation and formation of new businesses including small to medium enterprises. The report provides valuable insights into the ethical, legal and social implications (ELSI) of genetics and genome work in South Africa and sets out a number of recommendations to address the challenges. This document may also serve as a model for international stakeholders.

The ELSI of genetics and genomics impact on all. One of the recommendations is for the development of a code of conduct and best practice for professionals working in the field of genetics and genomics in South Africa to ensure that the work is conducted with integrity, honesty, collegiality, accountability and sharing. The findings and recommendations of this study are thus likely to be of interest to a wide-ranging audience, over and above policymakers and researchers.

The 13-member consensus study panel, under the leadership of Prof Michael Pepper, is to be commended on their diligence and on both the volume and quality of evidence that they have amassed to inform the recommendations they have made. This report is a product of their voluntary commitment and I thank them for their dedication to the task and look forward to the debates that will ensue following the release of the report.

I thank all those who were involved in the preparation and production of this report, particularly the Academy staff that supported the panel in their work. The ASSAf Council would like to extend its sincere appreciation to the panel for the service that they have rendered to the Academy. Funding from the Department of Science and Technology is also hereby acknowledged.

**Professor Jonathan Jansen**
**President: Academy of Science of South Africa**

# Acknowledgements

This consensus study report is the result of the collaborative work of many people who are acknowledged as follows:

Panel members: Prof Michael Pepper, University of Pretoria (UP) (panel chairperson); Prof Collet Dandara, University of Cape Town (UCT); Prof Jantina de Vries, UCT; Prof Ames Dhai, University of the Witwatersrand (Wits); Prof Melodie Labuschaigne (formerly Slabbert), University of South Africa (Unisa); Dr Freddy Mnyongani, University of KwaZulu-Natal (UKZN); Prof Keymanthri Moodley, Stellenbosch University (SU); Dr Antonel Olckers, DNAbiotec®; Prof Anne Pope, UCT; Prof Raj Ramesar, UCT; Prof Michèle Ramsay, Wits; Prof Himla Soodyall, Wits; Prof Wayne Towers, North-West University (NWU). These members contributed their time and expertise to this study on a voluntary basis. They are sincerely thanked for their highly valuable input and commitment to ensuring that the best interests of the country were always of paramount importance in all of their deliberations.

A special thank you goes to the group who wrote the report comprising Prof Anne Pope, Dr Antonel Olckers, Prof Jantina de Vries and Prof Michael Pepper, and also to Prof Ames Dhai who oversaw the Relationship Building Group, Dr Freddy Mnyongani who oversaw the Respect for Persons Group and Prof Anne Pope who oversaw the Good Stewardship Group.

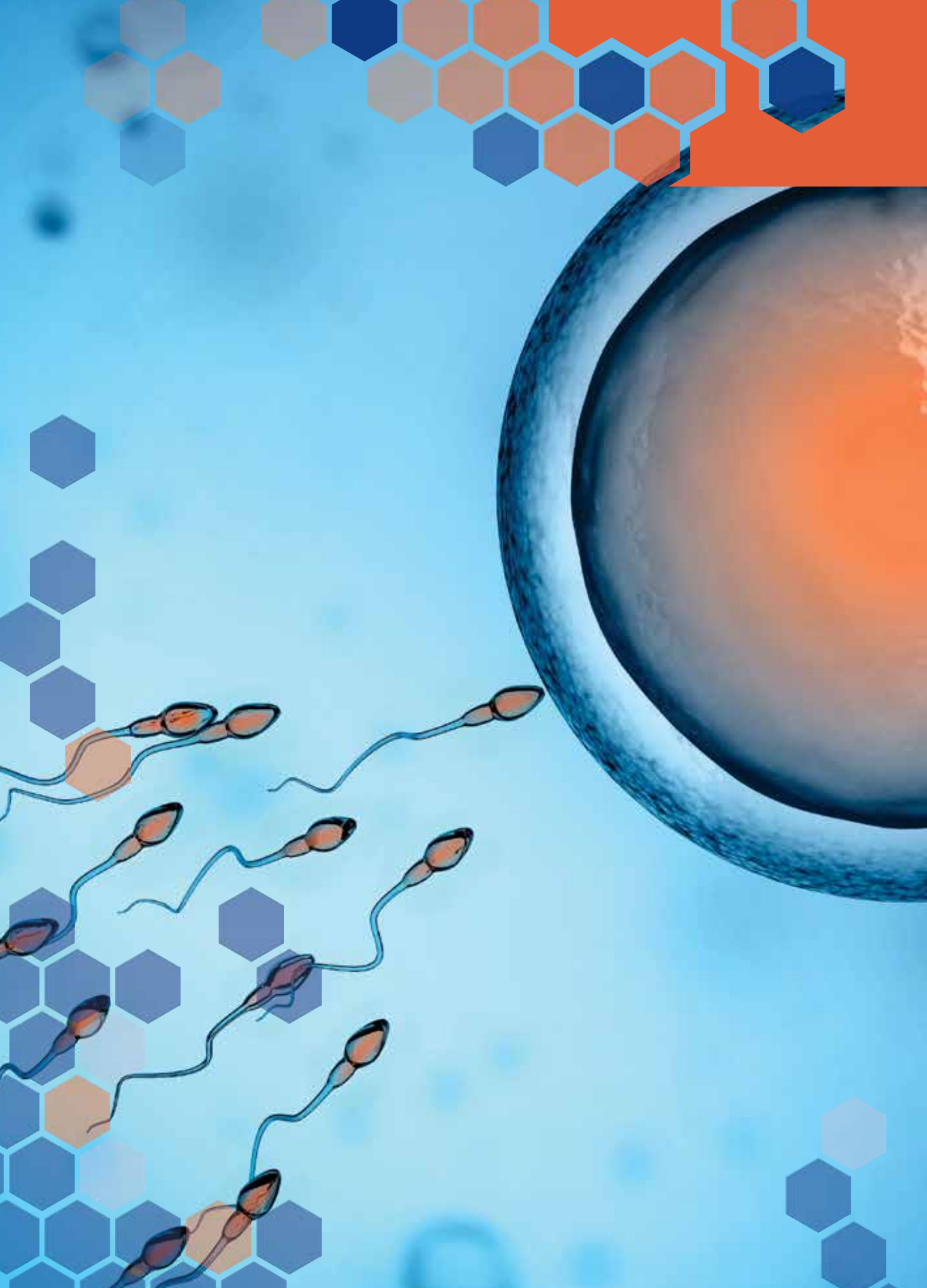
As part of the information gathering process, six consultative workshops were held with the following groups: The pharmacogenomics community, genetics service providers (two meetings held at Wits and UCT), the forensics community and the rare diseases community and advocacy groups. All participants and contributors are gratefully acknowledged. In addition, a presentation and discussion took place at the 2017 Joint Meeting of Research Ethics Chairs and the National Health Research Ethics Council in Pretoria.

The report was peer-reviewed by: Emeritus Professor Daniel Ncayiyana, UCT; Professor Ma'n H Zawati, McGill University; The National Intellectual Property Management Office; Mrs Glaudina Loots and Ms Modiegi Selematsela, Department of Science and Technology (DST). Their valuable suggestions are gratefully acknowledged.

Support and contributions from Academy staff, Dr Khutso Phalane-Legoale, Prof Roseanne Diab and Mr Ian Shendelana, are highly appreciated. Ms Patsy Scholtz is thanked for the editing and production of the study report.

The DST is sincerely thanked for providing financial support.

**Prof Michael Pepper**
**Panel Chairperson**



# Executive Summary

This study aims to address the ethical, legal and social implications (ELSI) of genetics and genomics work, as it relates to research, health service provision and forensic applications (medical and legal) in South Africa, as outlined in sections 1 and 2. The study was undertaken by a 13-member panel appointed by the Academy of Science of South Africa (ASSAf).

The deliberations in this report are centred on the broad philosophical approach of Ubuntu, a philosophical notion that refers to the essence or quality of being human (section 2.4, page 24). The report describes the benefits to be derived from genetic and genomics work, the need for boundaries to be clearly defined and adherence monitored to ensure that benefits are shared by all and that no harm is done. The report is divided into three thematic areas: Building Relationships (section 3, page 29), Respect for Persons (section 4, page 41) and Good Stewardship (section 5, page 69). Each section is followed by recommendations **(Recommendation R1 to R19)** which are ethically and legally sound, culturally appropriate, feasible, enforceable and sustainable, given the resources within the country, and balanced against competing national priorities.

The report commences with a brief study background (section 2, page 19), the study rationale, methodologies and some insights into the field of genetics and genomics. It highlights South Africa's current legislation on genetics and genomics and further highlights the absence of regulation in highly topical fields such as gene editing.

Section three (page 29) titled Building Relationships focuses on the engagement between human genetics and genomics practitioners and the general public. This relationship ranges from academic research projects, to genetic testing in the private sector, but also includes the relationship between the public, the law and the forensic science sector of the country. It highlights South African experiences with community engagement for genomics and the importance of education and the translation of science. It further stresses the critical role that persons with vested interests in genetics and genomics have to ensure that the public is well informed on research projects, their roles, rights and responsibilities. Four recommendations **(R1 – R4)** are made for building relationships and community engagement:

## R1. Stakeholder engagement (See page 38)

a) Promote understanding that a community (engaged in a specific research study) and the public at large are complementary stakeholders and that the development of engagement strategies needs to be considered separately for the two groups.

b) In genetic and genomic research, reciprocal researcher and community relationships should be promoted though community engagement activities such as the use of meetings with gatekeepers, establishment of community advisory boards (CABs) and the implementation of the principle of participatory action research.

c) The success of stakeholder engagements should be objectively evaluated on an ongoing basis by researchers and communities, or the public.

## R2. Education and training (See page 38)

a) Implement effective measures to improve the public's knowledge and understanding of genetics, genomics and associated new technologies in a culturally sensitive and appropriate manner.

b) Mere adherence to process is not sufficient; substantive engagement is necessary between researchers on the one hand, and their funders, the regulators, their ethics committee and research communities on the other.

c) Liaise with the Department of Basic Education (DBE) and the Department of Higher Education and Training (DHET) on how best to integrate information about new health-related technologies in school curricula.

d) Promote appropriate genetics and genomics training for health care professionals.

e) Make a substantive investment in training of genetic counsellors and clinical geneticists and other relevant professionals to increase the national capacity to deliver genetics and genomics services (See also **R14).**

f) Educate the public with regard to forensic deoxyribonucleic acid (DNA) testing.

g) Promote the integration of forensic DNA testing into the curricula of law degrees.

## R3. Protecting the public (See page 38)

Direct to consumer genetic marketing and testing must be regulated.

## R4. Accountability and transparency (See page 39)

a) Promote an appreciation and understanding of the importance of research for improving health care services for all while protecting public trust in the scientific fields of genetics and genomics.

b) Establish a clear and strong legal and ethical framework that includes

sanctions for misconduct in all genetics and genomics work, including commercial activities.

c) Ensure accountability and transparency in the practice of forensic science in all sectors (academic, public and private).

In section four (page 41), the topic of Respect for Persons is addressed in accordance with the South African Constitution, which recognises and protects both autonomy and self-determination in the Bill of Rights: the right to dignity (s 10), to life (s 11), to bodily and psychological integrity (s 12), which includes security and control over one's body, and, for women, control over reproductive decisions. It further highlights that legally and ethically, people are entitled to make free informed choices about their health care and research participation. The communitarian philosophical outlook and how it deepens respect for persons in Africa were taken into account. In this section the panel recommends the following **(R5 – R8)**:

## R5. Ubuntu philosophy (See page 66)

a) The Ubuntu principle must be promoted in genetics and genomics research, health care delivery and forensics practice.

b) Recognition must be given to the fact that while the concepts of autonomy and Ubuntu may be in tension, these are complementary rather than mutually exclusive principles and that all fundamental rights should be understood within the matrix of the community. Relative solidarity is an important component of Ubuntu.

## R6. Consent models for genetics and genomics work (See page 66)

a) Empirical research should be conducted to establish South African participant views on consent models.

b) It must be recognised that blanket consent is incompatible with South African legislation (e.g. The Protection of Personal Information (POPI) Act *(No 4 of 2013)*).

c) The National Health Research Ethics Council (NHREC) should be encouraged to prepare an informed consent template for genetics and genomics. The informed consent template should include the following considerations: whether results will be returned; benefit sharing arrangements; sample and data storage and re-use, including governance thereof; limits to the withdrawal of samples and data once shared; details regarding export of samples; privacy protection in countries to which data and samples are exported; and the specific circumstances that limit confidentiality related to DNA data.

d) The Department of Health (DoH) Guidelines on Ethics in Health Research (2015) that permit broad, tiered and specific consent models should

be fully implemented. The panel recognises however that there is lack of consensus regarding the impact of the POPI Act *(No 4 of 2013)* on broad consent, and that the situation may change once clarity is obtained from the Regulator.

## R7. Protection of information and resources (See page 66)

a) Oversight provided by Research Ethics Committees (REC) on future use of genetic material (samples and data) must ensure that proposals indicate whether storage is desired and if so, informed consent documents must include the relevant information to permit a voluntary informed choice by participants.

b) Researchers should not report their research findings in ways that may be, or may be perceived to be, harmful or offensive.

c) Engagement with the Information Regulator, Department of Justice, is important to discuss the development of regulations in the POPI Act *(No 4 of 2013)* and how this will impact on genetics and genomics research.

d) A policy should be put in place to guide decisions about disclosure of incidental findings (IF).

e) The challenges related to the timeframe of 30 days to remove a DNA profile from the National Forensic DNA Database (NFDD) should be revisited.

f) The establishment of a South African Human Genetics Advisory Board (SAHGAB) should trigger discussions with civil society with regard to the implications of forensic practices related to genetics and genomics, including the NFDD.

## R8. Communities, families and vulnerable and marginalised individuals (See page 67)

a) When working with small, identifiable groups that may already be socially or politically marginalised, researchers must include in the community engagement process a discussion on the manner in which the research process and outcomes will be managed to mitigate potential harm to the community, e.g. unintended perceptions of stigma.

b) Researchers investigating certain conditions, phenotypes or behaviours must also include in the community engagement process a discussion on the manner in which the research process and outcomes will be managed to mitigate potential harm to the community.

In the Good Stewardship section (section 5, page 69) the need for responsibility is highlighted in terms of sustainable and careful use of genomic resources

(reflected as both a value and a practice) by individuals, communities, organisations, companies and governmental institutions. This section is intended to emphasise the inherent characteristics of integrity, honesty, collegiality, accountability and sharing that make up the notion of stewardship. It further stresses the need for professionals in the field of genetics and genomics to take up the role of stewards in the interest of the people of South Africa, without fear or favour and to do so objectively. In section five, the following recommendations **(R9 – R13)** are made with regard to good stewardship:

## R9. Code of conduct (See page 91)

A code of conduct and best practice for professionals working in the field of genetics and genomics in South Africa should be developed by government and other appropriate entities to promote good stewardship of resources including data and biological specimens.

## R10. Policy and guidelines appropriate for the South African context (See page 91)

The following should be developed by government and other appropriate entities:

a) Guidelines for oversight of responsible clinical genetic/genomic testing, including for appropriate accreditation of laboratories offering genetic/genomic testing and for monitoring of staff qualifications and expertise.

b) An appropriate national policy that outlines considerations, obligations, mechanisms and circumstances for feedback of individual results.

c) Policies and guidelines to promote good stewardship of resources in clinical and research settings to promote innovation and translation of research into clinical practice.

d) A national framework for South African biobanks that includes integrated data storage systems that have the potential to enhance health care and justice (i.e. in forensic and legal contexts), and to maximise their value to society.

e) A national framework for sample and data access to promote equitable and responsible sharing of genetic and genomic resources to enhance knowledge generation and translational science, drawing on existing international and continental policies.

## R11. South African Human Genetics Advisory Board (See page 91)

A South African Human Genetics Advisory Board should be established. The board should have appropriate expertise to provide guidance to policymakers and regulatory structures (See also **R16**).

## R12. Open debate with stakeholders and policymakers (See page 91)

Debate, explore and adapt the 'sociologically informed model' for the principles of (a) custodianship/ownership of samples and (b) benefit sharing in South Africa. Include relevant stakeholders like the National Intellectual Property Management Office (NIPMO) and the South African Law Reform Commission, since the topics affect a cascade of implications: ethical values of equity and distributive justice; good governance principles of benefit sharing; whether intellectual property (IP) can exist if genomic resources are to be regarded as a 'common good'.

## R13. Legal framework (See page 92)

a) Laws and regulations relating to genetics and genomics must be aligned and contradictions must be carefully and comprehensively addressed.

b) The South African Health Products Regulatory Authority (SAHPRA) should regulate genetic tests under the Medical Devices Act *(No 14 of 2015)*.

c) The Criminal Law (Forensic Procedures) Amendment Act *(No 37 of 2013)* and its Forensic DNA Regulations (2015) must be updated.

d) The potential value of a mutually beneficial memorandum of understanding between the South African Council for Natural Scientific Professions (SACNASP) and the Health Professions Council of South Africa (HPCSA) must be explored for forensic practitioners using DNA testing (See also **R15** and **R18**).

A set of overarching recommendations (**R14 – R19**) is outlined in section six (page 93), as listed below:

## R14. Capacity development in genetics and genomics in South Africa (See page 93)

South Africa is currently in short supply of appropriately trained and skilled personnel at all levels of genetics and genomics work. To establish, build and maintain a service platform and large scale, sustainable genomics programmes for the benefit of a healthy nation, bearing in mind ethical, legal and social responsibility, will require technical, scientific, computational, bioinformatics and statistical analysis, as well as financial, legal and ethical expertise. More resources are therefore required to support genetic and genomic work, including training of genetics nurses, genetics counsellors, medical geneticists, medical scientists, bioinformaticists, biostatisticians and forensic scientists for the public and private sectors in South Africa (See also **R2 (e)**).

## R15. Legal framework with policies and guidelines for genetics and genomics in South Africa (See page 93)

Legislation and policies should be developed in an inclusive and cross-cutting framework, taking into account national, regional and international contexts, and should avoid stifling innovation (See also **R13** and **R18**).

## R16. South African Human Genetics Advisory Board (See page 93)

The South African Human Genetics Advisory Board (SAHGB) should be adequately resourced and independent, with the aim of providing oversight in genetics and genomics at the national level and working in concert with ethics and legal regulatory structures (See also **R11**).

## R17. Ethical oversight (See page 94)

Ethical implications that are deemed problematic by Research Ethics Committees, researchers, patients/participants or the public should be brought to the attention of the NHREC whose direct involvement in policy-drafting should be sought.

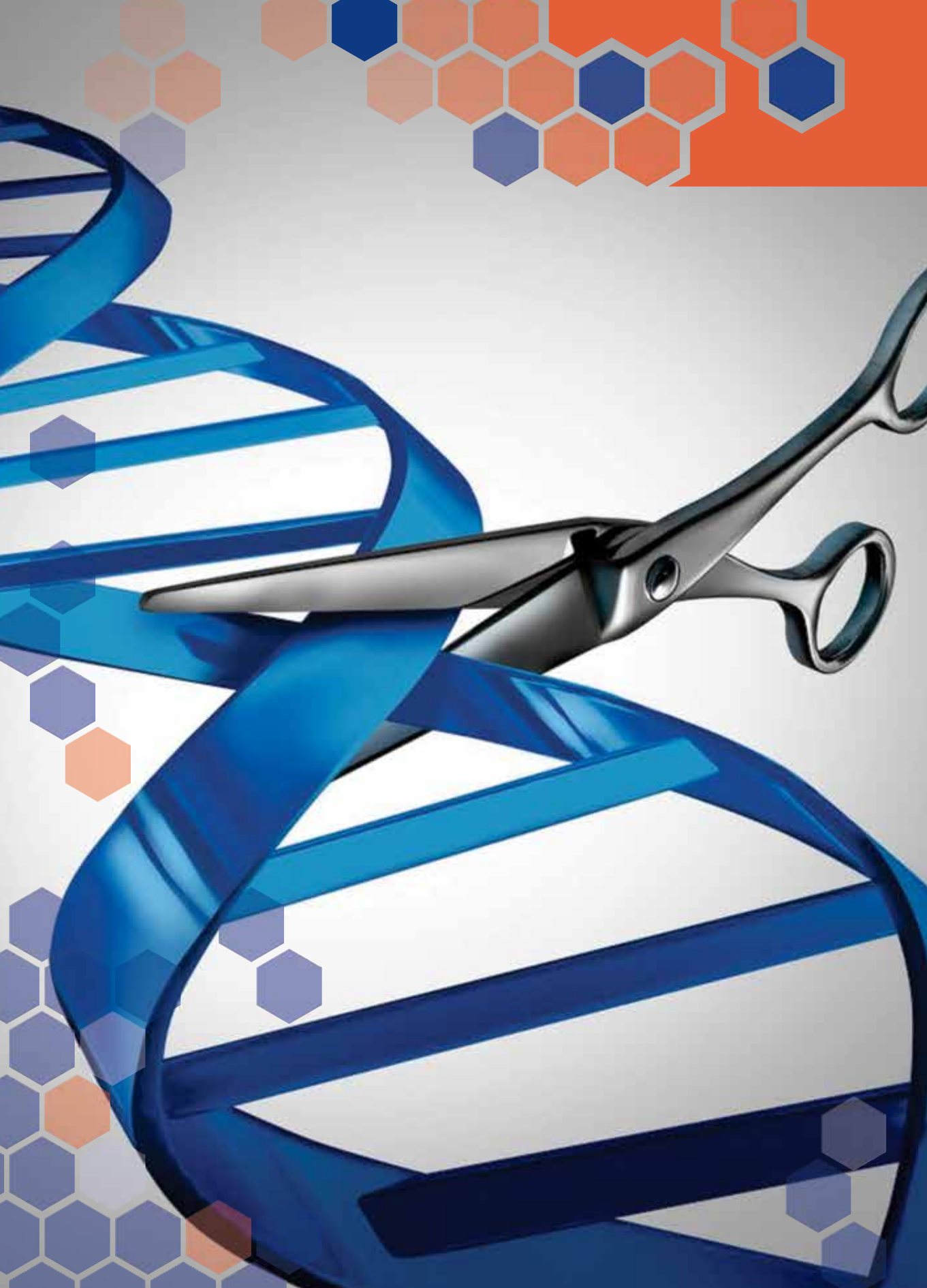
## R18. Legal oversight (See page 94)

Legal implications should be brought to the attention of the South African Law Reform Commission whose direct involvement in policy-drafting should be sought (See also **R13** and **R15**).

## R19. Framework for non-compliance (See page 94)

Sanctions for non-compliance with current and future legislation must be defined, be implementable and be effective.

In conclusion, this consensus report addresses the key imperatives in genetics and genomics ELSI and provides a set of recommendations which could inform the drafting of one or more policy documents. This in turn could guide the drafting of legislation, regulations and guidelines/standards to regulate genetics and genomics research, health care provision, forensic applications and associated areas in South Africa.



# 1 Preamble

We live in an era of rapid growth in the fields of genetics and genomics. Great benefit is to be derived from this work, which has the potential to impact positively on the health and quality of life of all members of society. Work in these fields is also likely to impact positively on the economy through job creation and the formation of new businesses including small to medium enterprises. For these benefits to materialise, however, skills development and clear guidance on how to implement these new and upcoming technologies are required. In addition, boundaries must be defined clearly, and adherence monitored to ensure that benefits are shared by all and that no harm is done.

Our objective is to produce an authoritative report that responds to these needs. While the fields are complex, our intent is to promote interest and encourage development of sustainable and ethical initiatives in the practice of genetics and genomics. Practice at this level includes clinical, research, entrepreneurial and forensic activities. Furthermore, genomic research is closely linked to biobanking and requires storage of samples and associated data sets, and therefore such activities are also included.

Focusing on South Africa and Africa in general, the broad philosophical approach for this genetics and genomics consensus study centres on Ubuntu, which is elaborated on in section 2.4 below. This theme guided deliberations and is central to the message conveyed herein. Within an African context, the self only makes sense in relation to the community. Incorporating a wide range of values, Ubuntu expresses the inextricable intertwining of the individual and his or her community. Key principles of human dignity and respect, as well as equity and distributive justice have also guided our deliberations. We were mindful of the need to ensure that the notions indicated in the title of this report, namely "Ethical, Legal and Social" implications, emerge as guiding principles, particularly regarding the more pragmatic areas such as informed consent, privacy, confidentiality, management of samples and data, intellectual property and commercialisation. The tendency to want strict regulation, due to past as well as recent adverse experiences, is understandable. However, we are conscious of the negative consequences that would flow from over-regulating the field, including stifling innovation and entrepreneurship.

The report is divided into three main sections, namely Building Relationships (page 29), Respect for Persons (page 41) and Good Stewardship (page 69), each of which contains a set of recommendations. The background to the study, rationale for the study and the methodology used are discussed in the next section.

# 2 Background to Study

From the moment of conception, deoxyribonucleic acid (DNA) dictates the nature of the structural and functional components that, once fully integrated, define who and what we are. Also contained within DNA is information that may indicate our predisposition to certain diseases, our potential to benefit from certain therapeutic drugs, and our ability to integrate into and function within the environment in which we live. While this information can be used to maintain health and manage disease for an individual or groups of people, it can also be misused and result in consequences that are detrimental.

Since the DNA of an individual is inherited from both biological parents, who in turn, inherited it from their biological parents, it is important to note that DNA is shared among biological family members. Also noteworthy is the fact that although an individual shares DNA information with family members, each individual nevertheless possesses a unique overall genome (except in the case of identical twins whose genomes are identical). That DNA is shared by biological family members raises the issue of the impact of discovery of any DNA sequences that may affect their health on the members who have not sought testing. With respect to confidentiality, this becomes problematic if some family members disclose information on their DNA that others do not wish to have disclosed. Furthermore, the information in DNA is often stored in databases, which can lead to some disclosure. Since an individual's genome is unique, if their data are in an existing database, a comparison to that database would identify a genetic match with high probability. Thus, access to such databases requires regulatory oversight.

Due to these unique characteristics of genetic and genomic work, there are unique ethical, legal and social implications (ELSI) that relate to this type of work. These ELSI could affect rights (to the extent that they exist), political capital, regulation and sharing. Conclusions inferred from research or testing results could be stigmatising or viewed as favourable or unfavourable at a socio-cultural level. A complication is that social preference in communities and nations is dynamic and changes over time, which necessarily requires regulatory mechanisms to be responsive to changing socio-cultural norms.

Finally, it is important to recognise that asymmetrical power relationships in science and medicine, together with historically unfair exploitation and data mining in Africa, especially where genetics and genomics are concerned, are important precursors to the ethical, social and legal dilemmas that exist in this field today.

## 2.1 Study Rationale

Currently, legislation in South Africa that deals with genetics and genomics is very limited. The National Department of Health (DoH) oversees implementation of the National Health Act (NHA) *(No 61 of 2003)* and its Regulations. Chapter 3 of the NHA mandates the Director-General to make provision for genetic services: "The Director-General must issue and promote adherence to, norms and standards on health matters, including – genetic services" (s 21(b)(vii)). Chapter 8 of the NHA deals with blood and blood products, assisted reproductive technology, cell-based therapy, transplantation, tissue banks and forensic medicine/pathology. Chapter 8 includes a section on reproductive and therapeutic cloning (s 57(1)(a) and (6)(a) & (b)) which states that manipulation of human genetic material from gametes, zygotes and embryos for purposes of reproductive cloning, is prohibited. The Criminal Law (Forensic Procedures) Amendment Act *(No 37 of 2013)* and its subsequent Forensic DNA Regulations of 2015 (*Government Gazette* 38561 of 13 March 2015, Government Notice R 207) only address the collection, use, storage, and destruction of DNA samples in forensics. The Medicines Control Council guidelines (August 2012) refer to genetically modified material including recombinant DNA technology in the section on biological medicines. Apart from the regulatory measures mentioned above, no specific legislation on genetics and genomics exists in South Africa. Thus, critical and highly topical fields of practice and research such as gene editing and gene therapy remain unregulated.

This document addresses the ELSI of genetic and genomic work, as it relates to research, health service provision and forensic applications (medical and legal). Many of the implications span all these areas, but some are specific to certain applications and will be indicated as such. For example, in a research setting, limited feedback of genetic results is provided to the participant, in line with the research design described in the informed consent documentation. In a clinical setting, however, a clinician must evaluate, often with the assistance of a medical scientist, what is of clinical relevance and utility and thus determine what is to be communicated to the patient or client.

The objective of this consensus study is to inform the drafting of policy documents, regulations and guidelines under the auspices of the DoH, the Department of Science and Technology (DST) and other relevant departments.

## 2.2 Methodology

This consensus study began with a proposal submitted to the ASSAf Council. Once the proposal had been approved, a team was appointed that defined the objectives of the study and met regularly over a two-year period to collect and deliberate on the materials collected from diverse sources. Several stakeholder workshops were held and included scientists, health care personnel, legislators, bio-entrepreneurs, research ethics committee representatives, as well as special interest and advocacy groups.

## 2.3 Human Genetics and Genomics

Human genetics and genomics are exciting and rapidly evolving fields, both in terms of the new knowledge generated and the rate at which such information is generated. Heritable traits, determined at conception, are transmitted through DNA from parent to child. "Genomics" refers to the totality of the information contained in the DNA of an individual as inherited from his or her parents, whereas "genetics" defines the field that applies this information in order to understand how characteristics of living organisms are transmitted from one generation to the next through DNA (i.e. the study of heredity). DNA information is useful in heredity studies in general, and specifically in the clinical setting in the management of heath and of individual identification as applied in forensics and kinship establishment. Human genetics includes the study of heritable factors in individuals, families and populations.

All cells in the human body originate from a single fertilised egg. As a result, every nucleated cell in an individual's body contains the same DNA which carries all the information required to form a fully functioning human being. DNA is found in the nucleus of every nucleated cell in the body. It is also found in mitochondria which are the energy producing organelles in the cell. Children receive half their genetic material from one parent and half from the other (nuclear DNA). Mitochondrial DNA is inherited from the mother. Regarding the sex chromosomes, daughters inherit one X chromosome from each parent, while sons inherit an X chromosome from their mothers and a Y chromosome from their fathers. The potential for genetic combinations is infinite, and each individual is therefore unique, the exception being identical twins who have identical DNA sequences.

The human genome is the entire heritable component with roughly three billion (a thousand million) DNA bases. Approximately 1.8% of the genome encodes protein-coding genes. Genes are the units of DNA that have a function and refer to segments of the DNA that code for products that function as either ribonucleic acid (RNA) or protein. According to the *Guidelines for Human Gene Nomenclature* (Wain *et al.*, 2002; updates available at https://www.genenames.org/about/guidelines), a gene is defined as "a DNA segment that contributes to phenotype/function". Epigenetics, which is the study of how environmental factors influence gene expression, is included under the umbrella term "genetic" in this consensus study.

Although the concept of a heritable unit or "gene" dates back to the time of Mendel (1822-1884), the structure of the DNA molecule was only elucidated in 1953. In 2003, the complete human genome was sequenced by determining DNA bases one by one. Since 2003, several incremental updates on the human genome reference sequence have followed. This is the global reference sequence, against which differences in individual genomes are measured. Research has shown that individual genomes differ from the reference sequence at roughly every 1 000 bases, with an average of three to four

million differences from the reference genome per comparative genome. Some differences have no effect on the phenotype of the individual and are referred to as neutral. Others are associated with disease susceptibility, disease causation and aberrant responses to therapeutic or recreational drugs.

Most typically, DNA is extracted from blood samples, dried blood spots, buccal swabs, saliva, tissue and even urine and stool samples. In forensic science, other sources have been validated e.g. bone, tooth pulp, dandruff and others. Once DNA has been isolated, it is robust and can survive intact for decades on a shelf, in a fridge or a freezer. The method of storage, however, will affect the quality of the DNA. DNA can be degraded by temperature, chemicals, contaminants, enzymes or other adverse environmental conditions. Since DNA is so robust, it has been isolated from individuals who lived tens of thousands of years ago. This is referred to as ancient DNA.

### 2.3.1 Applications of Knowledge in Genetics and Genomics

A key area of research in genetics and genomics aims to improve understanding of the relationship between genetic variants (sometimes referred to as mutations) and disease. In this regard, our knowledge and understanding have increased exponentially over the past decade, but still remain far from complete. In the field of human genetics, a distinction is made between disorders caused by mutations in a single gene (referred to as Mendelian or monogenic diseases or traits) and complex multifactorial traits (which are the result of a complex interplay between many genetic variants and environmental factors).

Over 3 000 monogenic disorders, including cystic fibrosis, haemophilia, sickle cell disease, muscular dystrophies and many more have been documented and the mutated gene that causes the disorder has been discovered. For most of the disorders, there are many different mutations in the gene that cause the disease. Sometimes they are limited to a specific family or population, while others are globally distributed (referred to as allelic heterogeneity). In other instances, groups of disorders with very similar clinical presentations are caused by mutations in different genes, for example albinism (referred to as locus heterogeneity). It is therefore important to understand the causal relationship between a variant or mutation and the disease in an individual patient, their family and sometimes in the population as a whole.

Complex multifactorial disorders are much more difficult to understand fully as they have both genetic and environmental (epigenetic) components. Genetic variants associated with a disorder are continually being identified. However, genetic variants that are markers of a disorder for one population may not be markers in another population. This includes disorders like diabetes, hypertension, asthma and most cancers. In these cases, a group of genetic variants can be tested and a genetic risk score calculated (provided enough information is available) to estimate the heritable portion of the risk. However, these variants tend not to be good predictors on their own; they do however

show some population and environment-specific properties. They should therefore be used in conjunction with family history, physiological biomarkers and environmental risk factors.

The use of genetic and genomic tests in the clinical setting is often referred to as genomic medicine and, more recently, as precision medicine. The latter notion is about more than merely heritable components and may be summarised as "making the correct diagnosis and identifying the most appropriate therapy that has the best chance of improving the health of the patient with the fewest side effects". The ethical, legal and social implications of precision medicine relate to health and wealth disparities, as well as generation of sufficient knowledge for implementation in understudied populations. Applications of knowledge in genetics and genomics that are not health-related include forensics or archaeological determination of human origins.

### 2.3.2 Global Genomic Diversity

All humans originated in Africa and then migrated to the rest of the world. Over time due to environmental pressures, different genetic profiles became predominant in different geographical locations. Because of population demography including migration, admixture, population size and isolation (e.g. cultural or geographic), populations have developed genetic signatures that continually change. These signatures can be used to place individuals according to their biological affinity into a specific demographic group, even when they self-identify culturally with a different group. Genomic results can also detect population admixture, while special analytical methods can calculate relative contributions of different parental 'ethnic' groups in admixed groups. Increasingly, however, due to genetics and genomics work, understanding is growing that almost all individuals have genetic signatures from different origins due to epigenetic influences. The concept of a 'pure' parental population or 'race' is therefore outmoded and no longer accepted as having scientific credibility. The current vocabulary of 'race', 'ethnicity', etc. is still in use due to lack of substitutes to express 'external differences' visible to the eye, that are still regarded as socially important in many parts of the world, including South Africa. The importance of genetic and genomic work which undermines these unscientific notions cannot be overstated especially for South Africa as it continues to work towards the goal of being a constitutional society based on respect, freedom and equality.

Genomic diversity refers to the number of variants in a given sequence relative to the human reference sequence. Many factors influence genomic diversity: one is the "age" of a population. Since the modern human arose in Africa and migrated from Africa in several waves, with some migration back into Africa, non-African populations tend to only have a subset of the variation present in African populations. Due to the ancient origins of populations in Africa, they have greater genetic diversity. In addition, frequencies often differ markedly within populations in Africa and when comparing African to non-African

populations. An example of the consequences of the above two factors is evident in a pilot study of the Southern African Human Genome Programme, which identified ~800 000 novel variants in just 24 South African participants (Choudhury *et al.*, 2017).

Due to the rich diversity, historically and presently, Africa is vulnerable to unscrupulousness with regard to data and sample mining via non-African funders that sometimes is undertaken without sufficient regard for the interests of those who provide biological samples or local researchers working in the various projects. This also occurs in projects in which biorepositories are established in Africa by foreign funders who allow preferential data and sample access to foreign researchers without sufficient regard for capacity building and collaboration where ethically appropriate.

## 2.4 Broad Philosophical Approach

In the 1990s, autonomy, privacy, equity and justice were prominent in discussions around genetic research (Knoppers and Chadwick, 1994). Traditional approaches to ethical concerns incorporated these four principles together with ethics theories based in Western philosophical thought. In particular, liberal individualism was prominent. Principalism was also widely promoted in ethics guidelines and discussions. Respect for autonomy created obligations regarding individualised consent processes, confidentiality, truth-telling and effective communication. Beneficence and non-maleficence required that risk-benefit assessments were carefully conducted on all research and that harm was avoided. Justice raised concerns about equity, individual rights and fair distribution of limited resources.

However, genetics and genomics, by definition, involve families, communities and population groups: a genetic disease affects an entire family, not just an individual. A genetic diagnosis in an individual necessarily has implications for other family members and a genetic result for one person may indirectly reveal the genetic diagnosis of another biological family member. Similarly, some communities may have a higher incidence of certain diseases, and the effects of genetic attribution to population groups may affect all members of those groups. In the context of genetic and genomic research, responsibilities and duties to family members, communities and even population groups become as important as responsibilities to individuals. A communal approach to the ethical challenges in genetics and genomics is therefore both relevant and applicable. Furthermore, the expansion of genetic research to population-based studies prompted bioethicists and scientists, over a decade ago, to revisit "the paramount position of the individual in ethics" (Knoppers and Chadwick, 2005).

Since 2005, Western philosophers have described the common good approach in genetics and genomics as an emerging trend in bioethics. Different ethical norms began to emerge such as reciprocity, mutuality, solidarity, citizenry

and universality (Knoppers and Chadwick, 2005). Reciprocity referred to the bidirectional relationship between research participants and researchers, one feature of which relates to the introduction of participant choice about whether to bank DNA and to allow future research. Prior consultation with communities was encouraged against a backdrop of dialogue, communication and transparency. Mutuality also emerged as an important concept in genetics with respect to sharing of genetic information with family members. Solidarity marked a 'communitarian turn' in ethics in the context of the right to know or not to know and the duty to make responsible decisions with respect to reproductive choices and predictive testing. Self-interest appeared to be subsuming to a willingness to share information that would benefit others. Citizenry was proposed to encourage public understanding of science in pursuit of the goal of promoting universality, i.e. the idea that all people should contribute to science and health improvement (Knoppers and Chadwick, 2005). However, despite this evolving 'common good' narrative, most ethics guidelines remain focused on the individual in research, science and clinical care. Given the significance accorded to informed consent, this apparent dichotomy is not conceptually contradictory. In South Africa, where community consent is required, individual consent is always required in addition.

It is interesting to note that the emerging communal trend described in Western philosophical literature in 2005 has since time immemorial been part of African philosophy. The African continent comprises several countries and cultures with heterogeneity of socio-cultural systems and worldviews. However, there are common aspects amongst these rich and varied cultural systems. Accordingly, Murove (2009) writes that the commonalities in the African cultural system include "a belief in ancestors, an understanding of an individual as communally constituted, and a relational world view". African philosophy provides "a conceptual interpretation and analysis of human problems and human experience in the African context" (Letseka, 2000). In this regard, the concept of Ubuntu plays an important role. Ubuntu is believed to be an Nguni word that "represents notions of universal human interdependence, solidarity and communalism which can be traced to small-scale communities in pre-colonial Africa, and which underlie virtually every indigenous African culture" (Roederer and Moellendorf, 2004). This characterisation is contested by some who believe that the origin is older and is from West Africa amongst Bantu-speaking people, and that Nguni languages have incorporated a variant of the word. There are similar words in African languages throughout sub-Saharan Africa, and the idea of Ubuntu is shared by many different indigenous groups on the continent (Kamwangamalu, 1999). Generally, there seems to be agreement among scholars that Ubuntu encompasses a wide set of values. According to Nussbaum (2009), Ubuntu "is the capacity in African culture to express compassion, reciprocity, dignity, harmony and humanity in the interests of building and maintaining community". Similarly, for Kroeze (2002), Ubuntu has elements of "communality, respect, dignity, value, acceptance, sharing, co-responsibility, humanness, social justice, fairness, personhood, morality, group solidarity, compassion, joy, love, fulfilment, conciliation".

Within an African context, the self only makes sense in relation to the community, hence the much-used Nguni saying that "umuntu ngumuntu ngabantu – a person is a person through other people" (Nussbaum, 2009; Murove, 2009). As Dolamo (2013) writes, "The cornerstone of Ubuntu as a core value in African ethics is the community. Individuals cannot survive outside of their respective communities in as much as fish cannot survive outside water". In an African context, community life is not optional for the individual (Himonga *et al*., 2013). Within this matrix, the community becomes a point of reference for understanding the self in relation to wellness, sickness, life and death. Since the community consists of the living and the living dead, the task of the individual is to maintain a good relationship with the visible and the invisible worlds (White, 2015). Taboos are an important aspect of community life as they signal what is morally acceptable and what is not. In this context, as White (2015) writes, illness may befall an individual because of failure to avoid the taboos of the community. Conversely, good health may be enjoyed by those who adhere to the cultural norms and avoid taboos of the community. Death, on the other hand, constitutes a constant threat to life (Mnyongani, 2012).

In the context of health care and health services in South Africa, Ubuntu has contributed to benchmarks, such as Batho Pele* (meaning people first) which are founded on moral values of respect for persons, truthfulness, courtesy, redress, openness and transparency. The Batho Pele principles pertinent to this project are consultation, service standards, access, courtesy, information, openness and transparency, value for money, encouraging innovation and rewarding excellence. An Ubuntu philosophical approach to research ethics and service delivery adds important values that should guide the conduct of research and health care in general, and genetics and genomics in particular (Metz, 2010). On the one hand, it suggests that there ought to be broad support for sharing of results of genetic testing with family members in the clinical setting and also for sharing genomic data and samples to promote secondary use and potentially beneficial research. However, such a framework also prescribes that where sharing happens, samples and data need to have been collected with consent that allows for such sharing and re-use, otherwise, by Ubuntu, there would be a failure of donors and researchers to share in a way of life. Similarly, where sharing happens, it needs to happen in the context of a reciprocal relationship. In other words, there needs to be some way in which sharing and secondary use promotes the well-being of the individuals and communities who have donated samples to projects. This has implications for benefit sharing in research and avoidance of exploitation of all vulnerable communities.

The emphasis on respectful relationships re-enforces the critical importance of genuine and effective community engagement as being essential for genomics and genetics research and health care services. Such engagement should aim to build trust and communal relationships between researchers,

* Batho Pele – Sotho for People First. It is a South African political initiative first introduced by the Mandela Administration on October 1, 1997 to stand for the better delivery of goods and services to the public.

practitioners and the community. It should also find ways to conduct research and deliver care that preserves and promotes community dignity and that is respectful of the ways that people within the community interact (be that in terms of language, social hierarchy or other dimensions of social interaction pertinent to health care and the research process).

The centrality of reciprocity in Ubuntu philosophy has implications for how research is conducted, who conducts it, and how it affects participants and their communities. It places importance on considering how research can practically improve the lives and well-being of community members. This could be done, for instance, by using the results of research to influence health policy, with the aim of improving health care for and well-being of community members. It could also mean that researchers need to consider sharing more tangible benefits that promote community well-being, for instance in the form of ancillary care or educational opportunities for community members. Reciprocity seems to increase incentives for the development of clear benefit sharing agreements before research starts. Finally, it increases the importance of ensuring that research contributes to capacity building. By respecting the concept of Ubuntu, one develops humanness by helping others to fulfil their own potential, and also by enabling local researchers to make contributions to their societies. This has implications for the role of international partners in health research and service enterprises. It also has implications for the potential commercialisation of genomic resources, which Ubuntu would consider to be public, not private, property.

# 3 Building Relationships

The focus of this section is on public engagement and community engagement. These terms are sometimes used interchangeably. They provide flexible umbrella terms to encapsulate the wide range of objectives, approaches and activities that might be employed as part of engagement efforts regarding the ELSI of human genetics and genomics (Burchell, 2015).

## 3.1 Public Engagement

For purposes of this discussion, 'public engagement' refers to engagement between human genetics and genomics practitioners and the general public. This can range from academic research projects to genetic testing in the private sector, but also includes the relationship between the public, the law and the forensic science sector of the country.

The 'public' has a diverse composition, i.e. it may be regarded as an undifferentiated whole comprising many different groupings, communities and people who comprise a diverse and complex population, or it can refer to different sections of 'the public' which may nevertheless be differentiated (Aggett *et al.*, 2012).

In South Africa, persons with vested interests in genetics and genomics activities, include people from research institutions, the private sector, civil society and policymakers, with varying degrees of knowledge and understanding of the field. An informed public is critical for successful work in genetics and genomics. It is vital that sufficient opportunities are made available for interested persons to become informed.

Many questions arising from current genetics and genomics research and clinical practice remain unanswered; e.g. how to facilitate meaningful engagement with the public and how to build capacity in genetic literacy and understanding of science, especially for people with generally low literacy and education levels (Leclerc-Madlala *et al.*, 2009).

Methods that could be used to facilitate public engagement are for instance social media, traditional media like radio and newspapers, crowdsourcing activities, discussion forums including, for instance, science cafés and possibly more creative approaches, such as comic books to explain key principles important to genetics and genomics practice (Botswana/Baylor Children's Clinical Centre of Excellence, 2016).

Importantly, public engagement should not be regarded as a way to fill the gap in people's knowledge to ensure they agree to what is being suggested. This model of public engagement, called the Knowledge Deficit Model, holds that, by informing ordinary people about new technologies, i.e. diminishing their knowledge deficits, they will be receptive to ideas about how to use them. However, this is not enough as ethically more is required from public engagement and the better view is that it concerns "sharing and exchange of knowledge, perspectives, and preferences between or among groups who often have differences in expertise, power, and values" (National Academies of Sciences, Engineering and Medicine, 2017).

## 3.2 Community Engagement

While a standard definition of 'community engagement' exists, developing a standard definition of 'community' is not easy because of multifaceted dimensions and variations of communities within and between contexts. Aggett *et al.* (2012) refer to a 'community' as a small or large social unit that shares values, norms, identity, cultural or religious beliefs which give rise to a shared understanding of what is needed for their well-being. 'Community engagement' indicates engagement between researchers and members of a community more directly affected by the research project with the aim of addressing issues like how to plan the envisaged research for their context, what role community members will play and how to bring the information to those who will choose whether to participate in the research study. Sometimes a community may be territorially defined or even exist in the virtual space of the internet.

It is important to bear in mind that communities are not static and members do not always agree or have common agendas. Tindana *et al.* (2007) warn against using the term 'community' to describe people as a community just because they live near one another, because this fact is not necessarily determinative of a 'community'. Geographic proximity does not prevent differences in value systems or other characteristics relevant to the social notion of community. Similarly, communities with distinct values and aspirations may inhabit a single geographic area.

The defining feature of 'community' is the common self-identification shared by its members. Thus, an individual may belong simultaneously to different communities: religious, vocational, or ethnic. Important in the research context is that 'community' may be defined by a particular disease. However, for the purposes of this consensus study, a specific definition of community will not be used.

A multidisciplinary approach is a key component of effective public and community engagement whether it is aimed at disseminating new information or conducting research planning sessions. Disciplines including sociology, anthropology, political science, organisational development, psychology, social

work, and many others contribute to improved levels of engagement (Minkler and Wallerstein, 2011).

## 3.3 The Goals of Engagement

In line with Ubuntu, and its emphasis on respectful relationships, genuine and effective community engagement is essential for genomics and genetics research and health care services. The aim of such engagement is to build trust and communal relationships between researchers, practitioners and the community (See section 2.4). In the research context, involvement of community members helps to promote ethically sound research practice (WHO, 2008; Akugizibwe and Ramakant, 2010; Bandewar *et al.*, 2010; Boulanger *et al.*, 2013). Generally, two primary goals of engagement can be identified; each has a different point of departure and pursues a different goal. Public engagement generally is about providing information to the public about new technologies, e.g. for genetics and genomics work, what the benefits of using the new services are likely to be, how to access them, clarification of expectations to diminish misunderstanding, and increasing knowledge and understanding as widely as possible. The goal is to provide the specific knowledge that the public is lacking with a view to promoting acceptance and use of the new technologies. This engagement should however not be coercive in nature.

On the other hand, engagement with communities begins because researchers are encouraged to work with the communities that will be requested to assist with research studies. The assumption is that research studies will be more ethical and more likely to achieve their objectives when participant communities contribute to the design and to organising how the study should best be managed in their social context. This engagement is encouraged as part of preparations and planning for the research studies. Here the goal is to gather information from community members about how to optimise the achievement of the desired research outcomes. Clearly, the two goals are different but they share the similarity of involving new information and the task of imparting it to people who are not familiar with the details of the subject.

While still in its relative infancy, over the last few years a number of theoretical and empirical papers have been published that explore the methods and goals of community engagement for genomics and biobanking research in Africa. Broadly, authors ascribe the following goals to community engagement in this context: to increase community understanding of the projects conducted; to strengthen the consent process by sensitising prospective participants before they are asked to enrol in research; to identify and respect community values; to assist in the design of culturally appropriate research methods; and also as a means for health education about the conditions in the genomic study (Tindana *et al.*, 2015; Singh *et al.*, 2017; Tindana *et al.*, 2017). One interesting approach to community engagement, which aims to augment the effectiveness of engagement activities in terms of all these stated goals, is to co-design community engagement and qualitative research in a community-

based participatory approach. Such an approach has been used in the context of genomics research on stroke patients in Ghana and Nigeria (Jenkins *et al.*, 2016) and is appealing for genomics research in South Africa too. Such an approach may have greater potential to influence the translation of research findings into health policy, and has greater potential to contextualise research than community engagement activities alone. Despite these broad goals attributed to community engagement, in the context of African genomics research community engagement seems to primarily be considered as a way to facilitate recruitment (Tindana *et al.*, 2015; Tindana *et al.*, 2017).

### 3.3.1 Rationale for Community Engagement

The goal of research in genetics and genomics is to understand the molecular basis of disease and to use an evidence-based approach to improve health and decrease the burden of disease. Moreover, advancement of locally relevant research is needed in South Africa, given its high burden of disease (De Vries *et al.*, 2011).

Community trust and involvement are critical to the success of this research (Moodley and Singh, 2016). Community engagement for research preparation encourages stakeholders to imagine new opportunities as they face new challenges. Tindana *et al.* (2007) assert that community engagement represents efforts to promote authentic and appropriate authorisation and permission for research to be conducted in communities, with appropriate levels of community involvement in, and ownership of, these activities. The goals of community engagement should ascertain the local relevance and social value of the proposed research, the ethical, cultural and practical acceptability of the proposed research, and how fair distribution of likely benefits of the research would occur.

Community engagement often raises the challenge of researchers' lack of fluency in the language of prospective participants. The importance of effective communication cannot be overstated and requires thoughtful and sensitive management. In addition to language, cultural expectations must be addressed appropriately. In many parts of the world, indigenous communities are regarded as 'vulnerable and marginalised', e.g. in the United States of America (USA), Canada and Australia, the Torres Straits Islanders and elsewhere. In South Africa, the majority of the population is vulnerable in clinical and research contexts for reasons of unfamiliarity with western scientific concepts, terminology, technologies and methodologies, as well as high levels of socio-economic disparity. Different language and ethnic groups have different expectations about whether and how outsiders are received and given access to community knowledge. The San Code of Research Ethics (South African San Institute, 2017) provides an example of an indigenous South African people's expectations of researchers who wish to involve them as research participants. The basic principles for their code are respect, honesty, justice, fairness, and care. These principles are elaborated on to express their expectations clearly and to inform the process for engagement.

### 3.3.2 Methods for Community Engagement

A range of methods is proposed for engaging communities in genetics and genomics research in Africa, including community meetings (Tindana *et al.*, 2012), community advisory boards (CABs) (Campbell *et al.,* 2015; Jenkins *et al.,* 2016) and multilayered engagement with stakeholders at different levels (Ramsay et al., 2016). One interesting idea is to draw on the enhanced research literacy of lay persons who are on research ethics committees as a resource for community engagement, and to act as a bridge for translating complex science into understandable terms and concepts (Folayan *et al.,* 2015).

Where projects use a CAB, such a board is assigned different roles. In the case of Campbell *et al.* (2015), the CAB served as a forum to discuss and identify pertinent ethical challenges arising in a psychiatric genomics project, and to assist in the development of recruitment processes and documents. In the case of Jenkins *et al.* (2016) the primary function of the CAB was to disseminate information about strokes.

A key challenge for community engagement activities is to design approaches for evaluating their effectiveness, partly because projects struggle to articulate clear goals for engagement (Campbell *et al.,* 2015). This largely leaves community engagement activities exposed to "trial and error" (Tindana *et al.,* 2017). On the one hand, there is need for a more systematic approach to community engagement, whereas on the other, there is the risk that community engagement becomes research in its own right, which would require ethics approval and informed consent and which, the Council for International Organisations of Medical Sciences (CIOMS) guidelines warn, would not be desirable (CIOMS 2016).

### 3.3.3 South African Experiences with Community Engagement for Genomics

Two studies have reported on South African experiences with community engagement for genomics research and biobanking. First, in a study exploring the views of 17 stakeholders involved in genomics and biobanking research in South Africa, Staunton *et al.* (2018) found broad agreement on the importance of community engagement in the research process, for reasons broadly in line with those given in the CIOMS Guidelines (CIOMS 2016) and the Joint United Nations Programme on Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS) (UNAIDS) guidelines (2012). Most importantly, interviewees considered community engagement important for intrinsic and instrumental reasons – because it operationalises respect for persons, can empower community members, and facilitates the research process. Importantly, community engagement was also considered an avenue for ensuring the feedback of generic study results to community members. With regard to engaging communities, interviewees described challenges in defining what constitutes a community in genomics and biobanking research, possibly because of the nature of this kind of research that only tends to

involve participants for a short while. Interviewees described the importance of education as a function of community engagement and proposed that education (and discussion about proposed research, presumably) would be one important way to allay fears of exploitation. In this study, community engagement was also seen as a way to identify, discuss and respect community values. High-level engagement with policymakers and regulatory authorities was also considered important to ensure the future sustainability of research, in terms of ensuring funding, infrastructure and appropriate regulation.

In a study exploring the genetic architecture of a psychiatric illness in a South African population, Campbell and colleagues set up a CAB to help discuss pertinent ethical challenges to their study and assist in the design of sensitive recruitment processes (Campbell *et al.*, 2015). Interestingly, this CAB blended psychiatric health professionals, patient advocates and community members. Many other genomic studies in the country have undertaken community engagement work in the context of genomic research, but these experiences are not published. In these initiatives, researchers have made use of existing community engagement infrastructure at research centres (Ramsay *et al.*, 2016), have embedded the genomic study as one aspect of a larger study which may have involved its own engagement activities (Zar *et al.*, 2015) or have organised health literacy days or used drama as a way of discussing illness with participants.

## 3.4 Education or Science Translation?

For the purposes of this discussion, 'education' refers to the development of innovative approaches to increase knowledge and understanding of genetics and genomics practice and research amongst the public. The public includes policymakers, health care professionals, biologists, end-users of genetic testing (e.g. the justice system) and social scientists. The aim is to ensure that they become more aware of the new knowledge and technologies, and of the opportunities and challenges they create. Systematic education incorporated into primary and secondary schools, as well as widely disseminated information aimed at the adult population, are urgently needed.

One of the main reasons that improved education regarding genetic and genomics is needed is the growing prevalence of direct to consumer (DTC) marketing of genetic/genomic testing. DTC marketing poses particular challenges for public education and the inevitable clash of interests between 'genomic entrepreneurship' and the public interest requires urgent attention. Traditionally, new health care services are accessible through trained health care professionals. This system is predicated on the understanding that health care professionals are appropriately educated and trained about the service being provided. A clearly established gatekeeping role is performed via this system, which has protection of the public interest in mind.

The major concerns with DTC marketing of genetic/genomic tests to the public are:

- That the results are provided directly to the recipient, without the assistance of a health care professional to translate the results to the recipient.

- That a considerable amount of data is obtainable from genetic testing, which needs extensive processing and validation before it is ready to be used as 'knowledge' relevant to the local context. In the setting where laboratory-based genetic services are offered directly to the public, it is not unusual that no appropriately trained health care professional is involved. This means that the interpretation of data may be incomplete or inaccurate, and when the information is passed along to the recipient, may cause significant anxiety and even harm.

- That the laboratory imparts genetic information about the occurrence of specific genetic variants which may imply an increased risk of elevated cholesterol, diabetes, cardiovascular disease or cancers, amongst others. Significantly, this information is based on interpretations in studies which track these genetic variants in populations in Europe and North America. Geneticists know that information based on these interpretations is not necessarily broadly applicable to populations of Africa or Asia. The clinical validity and utility in African or Asian contexts of genetic tests developed and understood in European and North American populations, especially for complex multifactorial disorders, such as diabetes mellitus and cardiovascular diseases, are questionable. The Southern African Society for Human Genetics (SASHG) has recently appealed to the public and clinicians to exercise caution when considering and interpreting these tests. The majority of these tests have not been scientifically validated in local populations, but are based on studies of populations of the northern hemisphere.

- That genetic and genomic data may be used irresponsibly by risk assessment businesses like insurers or others, which may lead to unlawful discriminatory practices. The situation is exacerbated by the lack of a regulatory framework for DTC genetic testing in South Africa to manage the risk of misuse or misdirected use.

The rapid changes in knowledge and technology, as well as the size of the genomics field, necessitates provision of context-dependent, just-in-time genomics education for clinicians and other point-of-care workers, e.g. through clinical decision support systems, including alerts and curated knowledge bases (Feero *et al.,* 2010). However, given the complexity of genome biology, clinicians and other health care workers must have solid foundational knowledge about genomics to understand and use the just-in-time material effectively. This means that the workforce must be adequately trained and educated in genetics. It is likely however that many health care professionals have limited genetics education.

Several forces drive changes in the genetics education environment including research technologies, regulations, health disparities, changes in health care institutions, the move towards personalised/precision medicine, the genetics workforce and clinician populations. Health care education, including genetics and genomics, should improve quality of care and patient health outcomes in general. The importance of genetics and genomics for nursing practice has been clearly identified and graduate nurses should be genetically literate, at minimum, to have a sound understanding of how genetics and genomics relate to and affect their professional practice (Giarelli and Reiff, 2012).

Knowledge requirements for all health care professionals should include a sound understanding of genetics terminology, inheritance patterns, diagnostics, family history assessment, screening, and how to make appropriate referrals. In addition, required skills include how to elicit a family history, how to identify the need for referrals, how to provide patient education (including credible sources of information), and how to assess the benefits and limits of genetic tests. Furthermore, a health care professional should understand the sensitivity of genetic information, appreciate psychosocial and cultural factors, and be knowledgeable about social, legal, and ethical concerns. Possible ways to address the need for genetics and genomics training for health care professionals include using online platforms. An example of a continent-wide initiative is the African Genomic Medicine Training Initiative (AGMT) for nurses involving genetics and genomics educators from across the continent (AGMT, 2016).

Developments in genetics and genomics occur very rapidly and bring with them new ethical, legal and social questions that need swift, sensible and responsible responses (Pepper, 2011). Examples include next-generation sequencing, genetic cohort studies and biobanks, which have raised questions about data management, including quality of interpretation of data, data storage, data sharing, consent for re-use of data, as well as concerns about identifiability and privacy interests of those who provide samples (Kaye, 2012; Wolf, 2013; Pinxten and Howard, 2014). However, the rapidity of advancement poses difficulties for those who must determine the responses to these questions. They are often slow or even overtaken by further advancements. Ethical, legal and social-related challenges should be prioritised for policymakers, researchers, clinicians and public health practitioners to maximise the benefits of genomic and genetic applications while minimising the risk of harm to people (Geller *et al.,* 2014). Any education strategy developed should therefore be dynamic.

### 3.4.1 Common Ethical, Legal and Social Challenges

Ethical, legal and social challenges can also arise in the context of discovering or receiving information about one's personal health status. The challenge for both the recipient and the person who communicates with the recipient is how to manage transmitting the information, how to 'package' the information, how to know whether the information is valid, properly analysed and interpreted,

and how to explain the options available for making treatment decisions and other choices. These challenges have a variety of ramifications.

Among the ramifications are that genetic information in a clinical diagnostic or even research setting may predict the future health of the individual, as well as their family members. Genetic information and choices in response to the information obtained in the present may therefore affect future generations. As such there must be clear guidelines in place to ethically manage data dissemination to patients and participants.

Genetic counselling is critical for the dissemination of genetic information. It is traditionally non-directive, which means that the 'counselee' must make up their own mind. This is consistent with the basic principle of respect for persons and the concomitant exercising of autonomy. For many people, the information provided by our invisible DNA is mysterious and intimidating, especially when it brings bad news about one's current or future health status. The challenge is to be supportive during counselling, to provide a clear picture of the options, to give sufficient information for decision-making, and to assist the person to come to a decision. Additional concerns arise when testing involves children about whether and how much to tell the child concerned, who should tell the child, what to do when parents do not agree about informing the child, how to help the family when a diagnosis is made, but no treatment is available, and how to integrate spiritual, indigenous and cultural needs into the counselling setting.

Similarly, in the forensic science sector, the challenge of data dissemination is complex. Education of the public and other role players in the justice system will be a major step in the right direction. Given the impact of forensic science on society, it is globally viewed as a field that should be practised with transparency and accountability. This is required as it leads to building trust between the government (public sector), the justice system and citizens of the Republic. This is in line with the several goals of the National Development Plan (NDP) of 2011 (National Planning Commission, 2011), in that it will enhance "effective social protection", redress "the injustices of the past effectively", will lead to an "effective and capable government" and also lead to enhanced "collaboration between the private and public sectors".

Research settings raise additional concerns that relate to the research process e.g. how will genomic data be interpreted; what will happen in the case of incidental findings and genetic variants of uncertain significance (VUS); will participants receive results when actionable variants are identified; and how will risk information be communicated to participants. Storage of samples and data also prompt specific concerns about possible ethical breaches including violations of privacy or confidentiality, security of databases against hacking, etc. As such, the possible identification of participants is a common source of anxiety and protocols are required to describe how this outcome will be avoided (Mathaiyan *et al.*, 2013).

## 3.5 Recommendations – Building Relationships

### R1. Stakeholder engagement

a) Promote understanding that a community (engaged in a specific research study) and the public at large are complementary stakeholders and that the development of engagement strategies needs to be considered separately for the two groups.

b) In genetic and genomic research, reciprocal researcher and community relationships should be promoted though community engagement activities such as the use of meetings with gatekeepers, establishment of community advisory boards and the implementation of the principle of participatory action research.

c) The success of stakeholder engagements should be objectively evaluated on an ongoing basis by researchers and communities, or the public.

### R2. Education and training

a) Implement effective measures to improve the public's knowledge and understanding of genetics, genomics and associated new technologies in a culturally sensitive and appropriate manner.

b) Mere adherence to process is not sufficient; substantive engagement is necessary between researchers on the one hand, and their funders, the regulators, their ethics committee and research communities, on the other.

c) Liaise with the Department of Basic Education (DBE) and the Department of Higher Education and Training (DHET) on how best to integrate information about new health-related technologies in school curricula.

d) Promote appropriate genetics and genomics training for healthcare professionals.

e) Make a substantive investment in training of genetic counsellors and clinical geneticists and other relevant professionals to increase the national capacity to deliver genetics and genomics services.

f) Educate the public with regard to forensic DNA testing.

g) Promote the integration of forensic DNA testing into the curricula of law degrees.

### R3. Protecting the public

Direct to consumer genetic marketing and testing must be regulated.

### R4. Accountability and transparency

a) Promote an appreciation and understanding of the importance of research for improving health care services for all, while protecting public trust in the scientific fields of genetics and genomics.

b) Establish a clear and strong legal and ethical framework that includes sanctions for misconduct in all genetics and genomics work, including commercial activities.

c) Ensure accountability and transparency in the practice of forensic science in all sectors (academic, public and private).

# 4 Respect for Persons

The point of departure for addressing respect for persons is that we accept that the communitarian philosophical outlook, including Ubuntu principles, informs our approach to this matter. Understanding and embracing this communitarian approach deepens respect for persons in Africa. The South African Constitutional Court has emphasised that constitutional values are to be interpreted through the Ubuntu lens (Makwanyane, 1995). This means that this interpretation of respect for persons is universally applicable for the purposes of this report.

African culture places a high value on heritage which is passed down from one generation to the next. Among Africans, although varied in different groups, the family is generally a core unit in society. Thus, decisions that affect an individual are often canvassed first in the immediate family, then in the extended family and finally in the community, depending on the issues being dealt with. Historically, in Western bioethical thought, respect for persons has had a distinctly Kantian meaning, with a strong emphasis on autonomy as the key component of human dignity. This emphasis on autonomy or self-determination underpins the notion of individualised informed consent and the need to protect the person's confidentiality (Peterson-Iyer, 2008). The principle of respect for persons has been described as "avoiding the incorporation of persons as a means to an end and [embodies]…the primacy of respecting self-determination" (Fernandez *et al.,* 2007). However, recent research from sub-Saharan Africa describes the concept of relative solidarity that takes into account generational differences in self-interest and autonomy (Ogunrin *et al.,* 2018). Informed consent is one way to ensure respect for persons, who are capable of making individual choices and decisions as autonomous agents in clinical care and research contexts (Mathews and Jamal, 2014).

Traditionally, health care professionals, especially physicians, have tended to frame their obligations towards patients in paternalistic terms because of their Western-based training, and mostly this is argued as the obligation to do good (beneficence). More recently, the increased focus on individual human rights, autonomy and self-determination have led away from a paternalistic outlook to a model of autonomy. The autonomy model emphasises the quality of the patient's understanding of the treatment and procedures being offered (Carstens and Pearmain, 2007). At least, this is theoretically the prevailing model. However well-intentioned, paternalism inevitably retains a role in responsible health care so that people who do not know they need health-related assistance might be steered towards it. This is done in the interests of their well-being, and they are allowed to choose whether or not to accept assistance. The African system which emphasises the inclusion of family and community decision-making, bridges an individual's lack of understanding by allowing

them to benefit from other members who have a better understanding and who can assist in explaining the heath or research aspects under consideration.

The South African Constitution recognises and protects both autonomy and self-determination in the Bill of Rights: the right to dignity (s 10), to life (s 11), to bodily and psychological integrity (s 12), which includes security in and control over one's body, and, for women, control over reproductive decisions. Legally and ethically, people are thus entitled to make free informed choices about their health care and research participation. Their choice is whether or not to provide consent for treatment or participation in research.

There is increasing recognition that the centrality of individual consent as a pillar of research and clinical ethics creates tensions with a more communitarian (or Ubuntu) worldview, in which decision-making processes often involve groups of people. The singular focus on informed consent has led to the perception that researchers are obliged to follow individualised informed consent and confidentiality processes, among others, to the detriment of more communitarian or community-based approaches that equally respect participants and human dignity. Yet culturally, in South Africa, many ethnic groups regard the family or community as central while also respecting individual choices. Necessarily, thus, most important decisions are taken in consultation with the family or community.

For respect for persons to be underpinned by Ubuntu, requires amongst other things, support for decisions to participate and the sharing of results from the participation (in this case mostly genetic testing) with family members in the clinical setting, and also the sharing of genomic data and samples to promote secondary use and potentially beneficial research. But such a framework also prescribes that where sharing happens, samples and data need to have been collected with consent that allows for such sharing and re-use, otherwise, according to the principles of Ubuntu, there would be a failure of donors and researchers to share a way of life in this context. Such sharing should be premised on a reciprocal relationship, in other words, sharing and secondary use should happen in a manner that promotes the well-being of the individuals and communities who have donated samples to projects.

In summary, respect for persons requires that the interests and rights of both the individual and the collective, specifically those relating to autonomy, privacy, confidentiality and access to the benefits arising from research results, are recognised and protected in a balanced, reasonable and justifiable manner.

## 4.1 Informed Consent

Informed consent is broadly described as "… that permission granted in full knowledge of the possible consequences …" either at individual or collective (community) level. While being mindful of the fact that relying on individual informed consent may be problematic in the context of communitarian

decision-making, it still has a role to play in respecting individuals. The informed consent process focuses on sharing information to ensure that the choice made by the participant or group is responsible and voluntary, free from undue influence or perverse incentives (Dhai and McQuoid-Mason, 2010).

Informed consent (HPCSA, 2016) encompasses two notions or objectives. The first is to 'inform' the participant or patient of the full implications of the study or procedure. The second is to obtain consent from the participant or patient to go ahead with the study or procedure based on the information provided during the 'informing' process. Both of these requirements need to be met. In the absence of being appropriately informed, consent is invalid.

The informed consent process for genomic studies starts prior to research, is on-going during the research and continues even after the research is over. Thus, this is not only an initial informed consent document, but rather involves frequent discussions with the research participant or patient. It starts at the time of community engagement and respect for persons would also require that participants are informed where possible about the results of the research. However, informed consent documents are the predominant means by which the wishes of researchers and research participants can be obtained and recorded (Kaye, 2012). A limitation of the once-off informed consent form is that researchers must anticipate all eventualities. By acting with consent, researchers can code research participants' data out of respect for these individuals (Knoppers and Chadwick, 2015). The emergence of biobanks attests to the impracticalities of obtaining individual consent from participants for every exact future use of stored data and samples. However, it is possible to give a broad area within which biological material or data can be used.

Genetic information, by its very nature, is personal, familial and communal. Our current lack of full knowledge of the extent of information contained in genetic material as well as ever-improving ways of characterising this genetic material requires that genetic materials and associated data be stored long term in biobanks, for future use. Biobanks are repositories where organised collections of human biological materials and associated data from large numbers of individuals are collected, stored and distributed for the purpose of health research. The potential uses of the information arising from the research must be discussed with the participants and should be incorporated into or addressed by the informed consent process. For example, due to new ways of genomic characterisation that are able to read every part of the genome, genetic variants known to be associated with genetic disorders need to be discussed with participants as part of their informed consent, as these variants, even where they are not the target of the research or clinical intervention, can be part of the incidental observations. Issues of participant's consent for sharing findings with blood relatives should also be discussed as part of the consent process.

One of the characteristics of genomic medicine is that information that arises is being decoded on an ongoing basis, with new information emerging all the

time. Thus, it is difficult to predict everything in advance. Due to technological advances and improved understanding, some information may only become evident years after original consent was obtained (Clarke, 2014). Informed consent for genomic analysis should preferably be a process of continuous interaction. Thus, it is important that mechanisms are put into place to ensure that there are processes or bodies to regulate the interrogation of new information that may not have formed part of the original consent. Dynamic consent processes and RECs that are trusted by researched communities through their broad participation, can be considered.

The types of information that participants need for valid informed consent must address both objective and subjective understanding (comfort) elements in order to comply with the ethics principle of respect for persons (Robinson *et al.,* 2013). New methods of consent will need to be created to replace blanket consent common to large-scale genomic databases and biobanks, with a consent procedure that gives participants control over what they might consider to be inappropriate use of their information and biological material (Greely, 2007).

Specific challenges exist with regard to obtaining informed consent in the context of genetic and genomic research. Some of these include cultural, socio-economic and educational differences between participants, communities, researchers and members of RECs. Researchers and REC members should be sensitive to the values, beliefs and attitudes of the persons from whom the materials are derived (Moodley *et al.*, 2014). The guidelines of the DoH (2015) refer to "an inevitable and unavoidable overlap between clinical and research domains" that arises with the use of data and human biological materials. This necessitates RECs to have comprehensive standard operating procedures (SOPs) to guide review of research that proposes use of human data or biological materials, including the need to ensure the integrity and comprehensiveness of the informed consent documentation. In particular, consent documentation must distinguish clearly between biological materials or data collected for clinical versus research purposes.

Written informed consent is required prior to removal of biological material from a living donor (NHA ss 56 and 62). In the case of a deceased person, consent to remove and use biological materials may be found in the will of the person, in a written statement or in a witnessed oral statement (NHA s 62(1)(a)) or may be provided by "the spouse, partner, major child, parent, guardian, major brother or major sister of that person in the specific order mentioned" (NHA s 62(2)). As biological specimens may be collected for diagnostic, therapeutic or health research purposes, research ethics committees should assess whether the nature of the proposed use of the samples is explained adequately so that the purpose for which consent is being requested is completely clear. The circumstances under which re-consent from donors would be sought should also be considered, taking into consideration specific local or national needs.

### 4.1.1 Consent in the Clinical Setting

A consideration of consent in the clinical setting is necessary for an investigation of legal and ethical issues relating to genomics and genetics. The reason for this is the increasingly closer relationship between health-related research and medical treatment, which in the future may become part of routine medical treatment and care. The evolution towards patient-centred medicine and patient-oriented research support this integration, despite ethical and methodological differences between the two. An understanding of these differences requires a grasp of the differences between the legal and ethical requirements relating to consent in the clinical, as well as the research context.

As outlined above, bodily and psychological integrity are protected by the law, including the South African Constitution, which means that when a health-related intervention is needed, the patient must, in principle, provide permission to violate bodily integrity to indemnify the health professional against a charge of assault. In addition, the permission should be given freely and voluntarily after the patient has considered the information and weighed the merit or lack of merit based on her/his own situation about whether to accept or decline the offer of treatment or other intervention. These considerations are consistent with the right to self-determination and to making choices freely, which are constitutionally protected in South Africa (Slabbert, 2011). The patient does not have to make a rational decision. Contrary to the views expressed by some scholars, a patient is free to make what others may consider to be an irrational choice. This freedom expresses the right to refuse treatment, which is also protected.

Special attention must be given to the requirements for consent by or for minors (i.e. a person not yet 18 years old) in the clinical setting, as provided for in the Children's Act *(No 38 of 2005)* (s 129). It must be noted that the requirements relating to consent for the research setting are completely different.

#### 4.1.1.1 Legal Nature of Relationship Between Patient and Health Professional

The legal nature of the relationship between patients and health care professionals is complicated in South Africa because of the dual health care system (private and public sectors) on the one hand, and because of the dual nature of the relationship between patients and health care professionals on the other. The relationship between a patient and a health care professional involves provision of services – relating to health care – which means the relationship is contractual. But, it also involves an agreement (not a contract) by the patient to permit his bodily and psychological integrity to be interfered with for the purpose of lawfully being able to touch the person to make a diagnosis and provide appropriate treatment. The terms of the service provision contract include (sometimes implicitly) the expectation that the health care practitioner will diagnose and treat the patient in accordance with generally prevailing and accepted health care standards and ethical norms (Dhai and McQuoid-

Mason, 2010). In addition, the contractual terms set out (sometimes implicitly) the quantum of the fee expected for the service. The contract also states the scope of the service and allows for the payment of diagnostic tests over and above the primary service fee. Clearly, this describes a private sector health care practice. In the public sector, the relationship between health care facility (clinic or hospital) and patients is also contractual but the terms are different. First, whether the patient has to pay a fee is determined by a means test, and second, all diagnostic tests are included in that fee.

In clinical genetics services, multiple role players are party to the informed consent process: the patient, her/his family, a clinician and usually, a genetic counsellor. Both pre- and post-test counselling occur, with the patient's consent for the genetic testing being obtained after pre-test counselling to ensure optimal understanding of the implications of the test and the procedures to obtain the necessary biological samples (McGuire and Beskow, 2010). It is important to note that, similar to other clinical interventions, genetic tests are conducted in the best interest of the individual patient or her/his family, based on the assessed risk related to a family history of genetic disease. The result may have implications for the patient and for biological family members. However, one salient feature after samples are taken from patients for clinical genetic testing is the duration for which these samples can be kept. A new phenomenon is that they can be accessed by other people for research when anonymised.

### 4.1.2 Consent in the Research Setting

For research involving genetics and genomics, the requirements for informed consent are like those for any other research that involves complex technical terms and concepts. The privacy and confidentiality interests of participants are often elevated as being of special concern for genetic and genomic research. However, the principles are the same as for other research: each person's personal and health-related information is private and must be kept confidential. However, particularly in the case of exome or whole genome sequencing, this must be balanced by a mechanism for traceability should an actionable incidental finding arise.

In principle, the requirements for enrolling participants in research on genetics and genomics are the same as for other research involving human participants. This means that a prospective participant must have enough appropriate information to assist her/him to decide whether to participate. Having acknowledged the dual nature of consent being individuality *versus* communitarian in the South African population, care must be taken to incorporate the appropriate type of acceptable consent for each group of participants even if they are all in the same study. Practically, this implies that individuals and their communities must both be consulted.

The nature of genetics and genomics research is such that genome sequences and genetic data from an individual are compared to large repositories,

databases or biobanks holding other similar data to identify genetic patterns and relationships (Knoppers *et al.,* 2014). Similarly, genomics research often involves the long-term storage of samples in biobanks for future use. Biobanks enable large-scale analysis of various diseases and health phenomena, but they also represent a link between abstract genomic data and concrete patient medical records (Peterson-Iyer, 2008). Most of the samples and data collected for genetic and genomic research are collected in the context of expectations that these resources will be made available for future use by third parties, either in South Africa or abroad. This poses real challenges for consent, namely that in the context of unspecified future use of data and samples, it becomes impossible to adequately inform participants of everything that will happen with their samples and data. Thus, it is important to build mechanisms of continuous contact with communities from which individuals are recruited, which can inform on the future use of their samples.

An important distinction can be made regarding re-use of samples in clinical work and research. Clinical work concerns the person who provided the sample, i.e. the re-use is for own use, e.g. further comparative diagnostic work. The implication is that further informed consent is not necessary on ethical grounds, since the person has provided consent for the sample to be taken and used for diagnostic purposes. However, when the sample is earmarked for research work, including for sharing with others, then the question of consent to re-use is relevant. It is in this context that different models of consent with varying degrees of scope have been suggested.

The nature of genetics and genomics work challenges the prominence of individualised informed consent, since as pointed out previously, this may have social and potential health implications for biologically related family and community members. In addition, while informed consent is of central importance to both clinical and research work, in the context of genetics and genomics, careful reconsideration of the model for informed consent is necessary to respond to the cascade of ethical issues that flows from a vibrant biotechnology industry (Kuszler, 2006).

In the context of research, the informed consent of the prospective research participant is needed. The South African Constitution provides in section 12(2)(c) that "no one may be subjected to medical or scientific experimentation without their informed consent". The NHA, and more specifically section 71, provides that "research or experimentation on a living person may only be conducted in the prescribed manner and with the written consent of the person after he or she has been informed of the objects of the research or experimentation and any possible positive or negative consequences to his or her health".

Persons above the age of 18 may consent independently to research, whereas children below 18 years of age need the assistance of their parents or guardian for their participation in research for a therapeutic purpose. In this case, the

consent of the parent or guardian of the child, and of the child itself must be obtained, if he or she is capable of understanding (s 71(2) of the NHA). Where children are to be included in non-therapeutic research (which is not designed to benefit the specific child participant), the consent of the Minister of Health is needed. This consent has been delegated to registered RECs in the country. Consent will be granted only in limited circumstances, for example, if it is shown that the research objects cannot be reached if the research is carried out on adults, and if the child is not to be subjected to significant risks. Another important aspect on consenting on behalf of children is the question of DNA sample re-use. What will happen when the child has reached adult age? Are mechanisms put into place to re-consent them or are they bound by decisions made on their behalf for the rest of their lives? This issue is relevant for population biorepositories in which samples are stored for long periods or indefinitely.

In the research context, informed consent serves to ensure that a potential participant has sufficient time to consider the relevant information about the proposed research and to choose freely and voluntarily whether to participate, as stated above. The DoH's guidelines on Ethics in Health Research: Principles, Processes and Structures (DoH Guidelines on Ethics in Health Research, 2015) provides a discussion on informed consent for South African-based research. Special care has to be exercised to ensure simple but effective and respectful explanations in the informed consent documentation. Readability scores for this documentation are very important to include in the materials made available to ethics committees.

Local litigation about informed consent in a research setting in South Africa is sparse. Venter v Roche Products (2014) is a landmark case. It is the first to deal with a claim by a research participant for compensation for non-medical harms that occurred as a result of participation in a clinical trial. The significance of the judgment is that it places firmly and clearly in the public domain the importance of the need for research participants to understand and appreciate the information provided as part of the informed consent process. It also illustrates that, despite a deliberate discussion with the researcher and time to consider the implications by discussing the matter with his wife, the participant did not fully grasp the significance of the information. First, the information about how to understand the risk of trial-related bodily injury that may occur and, second, how to understand the implications of the scope of the insurance cover offered by the sponsor of the clinical trial in the event that trial-related bodily injury should occur. The participant sued for pain and suffering, as well as loss of income, neither of which is covered by a clinical trial insurance policy.

#### 4.1.2.1 Legal Nature of Relationship Between Participant and Researcher

In the research context, which includes genetic and genomic research, the relationship between participant and researcher is the same in both the public and private health care sectors. However, instead of a service provision contract, the principal nature of the agreement between the parties

(participant and researcher) is one recording the agreement to participate, and the permission granted by the participant to permit interference of her/his bodily and psychological integrity to the extent described, in the information provided. One part of the consent document is contractual in nature, *viz*. the part that records the offer of insurance cover made by the sponsor, subject to terms and conditions. The insurance cover is to pay the costs necessitated should bodily injury to the participant occur as a direct result of trial participation. When the participant accepts the offer of insurance (signalled by the participant choosing to participate), that contract is complete. The rest of the consent document is a written record of the basis on which the participant agrees to participate and to allow his bodily and psychological integrity to undergo interference. It is important to note that even though the offer and acceptance of insurance cover to bodily injury as a result of trial participation is contractual, the rationale for making the offer does not flow from a legal obligation. Instead, it stems from a moral obligation agreed to by most people who sponsor and conduct clinical trials. The rationale is that, even though the research participant freely accepts the risk of harm inherent in the clinical trial, society cannot rightly permit that person to also bear the monetary burden of restoring health should bodily injury occur. This rationale fits with one of the models that explain why people (should) participate in clinical trials, *viz*. as an altruistic gesture to improve knowledge about health care.

#### 4.1.2.2 Prospective *versus* Retrospective Research

Retrospective research refers to research conducted on biological material or generated data that already exist. This existing biological material or data could have been generated from either clinical or research samples. There are conflicting views as to whether such research requires that participants/patients specifically consent to use of their data (Tassé, *et al.,* 2010; Moodley *et al.*, 2014). Ethical, legal and societal issues arise as to whether such sample (e.g. DNA) or data have been anonymised at the time of sampling and whether the patient was informed of possible research or future use. In some cases, to build a rationale for research, a patient's data that exists in their medical records is accessed before a proposal is submitted to ethics review. The need to make provision for exploring new questions that may arise has led to the rapid growth of bio-repositories, which in turn has required the promulgation of laws, regulations and recommendations. One of the issues related to these bio-repositories has to do with consent for the secondary use of DNA or data. While one can inform as much as is possible on prospective research to participants, once recruitment has been completed, and new questions become available and need to be answered from the same sample set, this genetic material already falls into the retrospective realm. The use of retrospective biobanks or samples could be regulated or policed by community trusted RECs, for any new relevant questions or utilisation.

### 4.1.3 Models of Informed Consent

A variety of consent options are available to researchers. This section describes the models, which include specific consent, tiered consent, broad consent, blanket, presumed consent with explicit opt out opportunity, waived and dynamic consent. The current South African position does not advocate use of a particular model for informed consent (DoH Guidelines on Ethics in Health Research, 2015). Instead, these guidelines explain the various options for consent and outline the factors to be considered to protect the interests of those who provide their biological samples. When considering informed consent, there are two factors that constantly need to be balanced, in terms of their expectations: (i) researchers or physicians; and (ii) research participants or patients. Researchers would mostly support processes that are less cumbersome and allow them as much use of the acquired genetic material as possible, while research participants are mostly concerned with benefit versus harm related to participation. Below, we give an overview of different informed consent processes.

#### 4.1.3.1 Specific Consent

The most restrictive model of consent to use biological samples is specific consent, which allows use only for the purpose stated in the consent form, whether for clinical or research purposes. Any further use requires the person to give new consent (McGuire and Beskow, 2010).

Researchers tend not to favour this model of consent because they argue that the costs involved in re-contacting and re-consenting persons are high. In addition, logistical difficulties may arise when people have relocated without updating contact details. These somewhat expedient arguments avoid addressing the main reason for informed consent which is to respect the autonomy of persons.

New legislation, the POPI Act *(No 4 of 2013)* requires persons to be given specific information regarding the use of their personal information, which means that this form of informed consent aligns most closely with the Act's requirement. The purpose of this statute is to safeguard individuals' privacy interests by preventing unlawful collection, use and dissemination of personal information, bearing in mind, amongst other things, that unnecessary hindrance to free flow of information including personal information would stifle economic and social progress.

#### 4.1.3.2 Tiered Consent

This form of consent presents a range of study procedures which may be selected individually. For example, tiered consent permits the person to choose whether to participate in the primary study, whether to permit storage and future use of their samples and whether to permit cell line creation. The extent

of the tiered consent depends on whether the person chooses not to permit a particular procedure. In the example, if the person chooses not to permit storage and future use of his samples, then the choice about cell line creation falls away, since it is dependent on the previous choice.

Each tier offered for consideration requires additional information to be provided, e.g. the storage tier must explain where and for how long samples will be stored and what happens to them at the end of the storage period. Tiered consent offers a blended model that combines specific consent and broad consent for the different facets of a research project.

A significant challenge with this model is that it is logistically very difficult to implement and thus to honour the undertaking implicit in the tiered consent arrangement, i.e. that further consent will be sought for the tiers that do not currently have consent. Tracking the samples and the donor become extremely difficult in the absence of widespread electronic communication networks. While this model appeals strongly to RECs and others who wish to address potential donors' unease with the implications of broad consent, it should be chosen cautiously. If the study is such that tracking and follow-up with donors will present logistical difficulties, then it should not be chosen because it would likely end up misleading participants that their wishes will be honoured when in fact they may not.

#### 4.1.3.3 Broad Consent

Broad consent describes the situation where, at the time of providing the sample, the person consents to general use of the sample for genetic and genomic research, including for unspecified future projects. An example would be a narrowly defined future use for certain kinds of research. In this case it must provide a description of the governance framework for access to the samples by third parties, including the need for further ethics review and approval for the proposed further use. The plan to use the broad consent model must include genuine community engagement before commencement of the research (Grady, 2015).

Concerns about this model include the fact that informed consent cannot occur because participants cannot be informed about the nature of re-use that may occur. The use of broad consent may be ethically appropriate for research that involves sharing and re-use of samples and data (Grady, 2015). The appropriateness of this model is seen to reside in the fact that it consents to a governance structure that relies on 'letting others decide' (Sheehan 2011a; 2011b). A paper reviewing evidence from African countries found no a priori reasons to reject the use of broad consent in African countries (Tindana and De Vries, 2016). The acceptability of broad consent is evident elsewhere too: the Declaration of Helsinki (2013) and the Declaration of Taipei (2016) both support broad consent for biobanks. Arguably, facilitation of further research with stored biological samples or data is a strong motivating factor.

In South Africa, the POPI Act *(No 4 of 2013)* limits further processing of personal information without consent. Section 15(1) indicates that further processing of information without consent is lawful if it is "in accordance with or compatible with the purpose for which it was collected".

In South Africa, the use of broad consent is not uniformly accepted. This is in part due to cultural reasons which would require use of a different consent model (Moodley and Singh, 2016). For example, the South African San Institute has drawn up a Code of Research Ethics that elaborates, from the San perspective, on five principles: respect, honesty, justice and fairness, and care. Researchers are expected to follow that code which customises the usual ethics guidelines so that San culture is appropriately respected (South African San Institute, 2017).

#### 4.1.3.4 Blanket Consent

Blanket consent is all-encompassing consent, i.e. open-ended and without limitations on the use of samples or data. Consent at recruitment to the study covers the present study and all future use and sharing without limits or restrictions. This model is not appropriate for South Africa on legal and ethical grounds: the law prevents open-ended consent for use of personal information, which includes medical information. The POPI Act *(No 4 of 2013)* requires voluntary consent that manifests an "expression of will'. Further, the purpose for which the information is collected must be specific, explicitly explained and lawful (s 13(1)). On ethical grounds, the blanket model is unsatisfactory because it fails to consider any of the usual ethical principles that underpin informed consent.

Nevertheless, researchers often defend the model for repository or biobank specimens because of the freedom of use it provides. However, the DoH Guidelines on Ethics in Health Research (2015) do not recommend blanket consent because application of fundamental ethical principles, especially respect for persons, when consent is open-ended and without limitation, is hindered. Furthermore, the model puts the balance of power in favour of researchers and managers of repositories or biobanks, while the interests of donors of samples are without oversight. Consequently, ethical values such as justice, equity, privacy, confidentiality, risk of harm and likelihood of benefit are not considered in this consent model. In addition, in South Africa's multicultural society different views prevail about the use of biological materials, and careful deliberation is always necessary when considering whether and how future use of materials may be achieved.

#### 4.1.3.5 Presumed Consent with Opting Out

This model presumes consent for future use and sharing of samples and data unless the contrary is expressly indicated. Allied to the notion of informed consent is the right to refuse. This right is protected by the option to opt out. However, for the South African context, the model poses significant challenges. Presumed consent must be communicated to the public so that everyone

knows about and understands that samples will be stored and re-used unless individuals explicitly opt out. A difficulty in multicultural multilingual South Africa where large segments of the population also have low formal educational and literacy levels, lies in the challenge of communicating the notions effectively. The ethical implications of ineffective communication and thus lack of understanding and acceptance are obvious: in the eyes of those who do not understand or accept the model, their protected interests would be violated if samples and data are stored and used without informed consent having been obtained.

The model permits collection and storage of (residual) samples and re-use of stored specimens in genetic and genomic research which is attractive as the resources increase with less effort required. It must be noted however that there is little local empirical evidence to show whether South Africans would accept such a model. Several South American low to middle-income countries (LMICs) such as Argentina, Chile and Colombia, use this model for collection of human organs and tissues.

#### 4.1.3.6 Waived Consent

Consider the following: archived samples exist for which consent for future use and sharing was not obtained, because, at the time they were collected, future research was not envisaged; or samples obtained with informed consent were stored and later re-use is desired. These samples and their associated data are a valuable resource for genetics and genomics work. The dilemma is how to manage the absence of consent for future use.

The DoH Guidelines on Ethics in Health Research (2015) permit RECs to exercise their discretion to waive the consent requirement in these circumstances. They state that RECs "may approve a waiver of consent for secondary use of material or data where no more than minimal risk of harm is likely; and the donor's rights and welfare interests are unlikely to be adversely affected; and the research cannot be conducted if the waiver were not approved". The discretion must be exercised systematically and pragmatically.

Important considerations for a waiver of consent include whether the original scope of consent envisaged future use of samples, whether harm of any type may flow from subsequent use of the samples, whether identifiers might be linked to the samples, and how this might be managed. In each case ethics review of future research is required.

#### 4.1.3.7 Dynamic Consent

This model emphasises continuous re-contacting of donors, to provide 'real-time' information about specific research projects and to seek consent to use their samples and data in each new research study. Participants retain direct control over their samples and data. Dynamic consent relies on electronic

communication methods like social media, websites or e-mails, to inform, and to offer further choices. The retained link between the donor and the sample and the frequent re-contact about re-use is favoured by some people. This model has not been tried in South Africa; given the method of communication envisaged, and it is unclear how effective this would be in our populations.

#### 4.1.3.8 No Consent

This model is the extreme version of the opt-out model of consent because it does not include the option to decline to have one's samples or data re-used. It finds its rationale in the argument that the requirement for consent for researchers to use biological specimens and data hampers scientific advancement and, in any event, does not guarantee participant protection (McGuire and Beskow, 2010). This model is not satisfactory for its failure to engage with the legal and ethical rationale for informed consent in the South African context.

#### 4.1.3.9 Discussion on Models of Consent

The DoH Guidelines on Ethics in Health Research, (2015) permit researchers and RECs to use the consent model that is appropriate for the context of a study. Thus, the specific consent, tiered consent or broad consent models may be chosen to optimise collection, storage and re-use of samples and data. Funders should not be permitted to dictate broad consent as a funding requirement. The guidelines remind us that the choice of consent model should bear in mind the overall societal interest in advancing knowledge to improve health through genetics and genomics through re-use and sharing of samples and data.

### 4.1.4 Challenges of Human Genetics and Genomics that Impact on Informed Consent

The above has alluded to some of the challenges relating to genomic and genetic research, which raise legal and ethical questions about human identity, privacy and confidentiality, inviolability of the human body, human dignity, autonomy, corporeality and ownership of human biological materials, and the benefits arising from research using human biological material. These challenges are not unique to South Africa but indeed prevail in research at the continental and global level (H3Africa, 2013). Some of these issues are discussed below.

Genetic material is passed on from one generation to the next and is shared to different degrees by family members. Thus, each test that is carried out on an individual provides a window into knowing the genetic constitution of their relatives and effectively, a window into the general genetics or genomic profile of the specific community. The question might therefore be asked: does DNA belong to an individual? What are the implications of a closely related family member having their genome characterised? Besides ownership, each genetic test comes with a myriad of challenges regarding the circumstances under

which such a test should be used, who has access to the test, what the results tell us or how the results affect the individual/community in terms of third parties such as insurers or employers regarding judgements based on genetic constitution. Responses to the above questions depend on the significance attached to autonomy, privacy and confidentiality. Another challenge pertains to the use of current technologies which have enabled deeper and more extensive genome analysis. This relates to the ability to share vast amounts of information on other/non-target positions on the genome, the so-called incidental findings. Should these be reported or ignored? This is discussed in section 4.4 (page 62).

## 4.2 Confidentiality, Privacy and Traceability

Maintaining confidentiality in the doctor-patient relationship is a time-honoured moral obligation and a hallmark of professionalism. This duty is enshrined in the Hippocratic Oath (Declaration of Geneva, 1948) and various professional codes of conduct. As such geneticists and genetic counsellors are bound by this duty. In research, confidentiality is maintained as far as is possible, but at a more diffuse level given the wide range of research stakeholders who have access to research data and health records. This must be disclosed to research participants as part of the consent process.

Privacy is a legal right to which patients and research participants are entitled. Protection of personal information is therefore a legal obligation. The legal landscape in South Africa requires a careful balancing of protection of personal information with the right of access to personal information and the right to freedom of expression. It is against this backdrop that disclosure is permitted but only if it is in the public interest.

The confidentiality and privacy of genetic information is a key priority in jurisdictions that regulate the disclosure of and access to personal information. The POPI Act *(No 4 of 2013)* places emphasis on the privacy of health and biometric information (including DNA) by denoting these categories as special personal information. Access to, and processing of such information, is limited to the health sector and should be in the best interests of patients and research participants. A possible threat to the privacy of personal information exists in instances where a person's genetic results are stored, processed or kept in a data bank by institutions or persons in the insurance or financial sector, health sector or the employment sector. In South Africa, the confidentiality of health information held by hospitals and other health establishments is protected in terms of section 14 of the NHA, which provides that no person may disclose any of this information unless with the consent of the relevant person, if required by court order or if non-disclosure constitutes a serious threat to public health. Moreover, privacy is also protected by both the South African Constitution in terms of section 14, as well as by common law (Neethling *et al.*, 2005).

The taking of a genetic sample of an individual, the genetic testing itself, the collection of and acquaintance with, as well as disclosure or publication of the results without the person's consent would hence constitute an infringement of both the right to privacy in terms of the common law and the constitutional right to privacy. An example of an invasion of a person's constitutional personal autonomy privacy right and informational privacy right is the taking of a person's blood for testing without consent (See the case of S v Orrie (2004) regarding the taking of a DNA blood test for criminal investigation). In addition, the Criminal Law (Forensic Procedures) Amendment Act and the 2015 Regulations contain provisions relating to the requirement of informed consent for the taking of samples, as well as access to information derived from the samples. Section 14(d) of the South African Constitution in addition refers to the "right not to have – the privacy of communications infringed", which would protect the privacy of any communication between a person undergoing genetic testing and his or her health practitioner, e.g. relating to a genetic result. In the sphere of an individual's private life, disclosure may have a profound impact. Does an individual have to disclose genetic risks to his or her family, spouse or partner?

Genetic information may lead to both direct and indirect forms of discrimination. Genetic discrimination refers to the situation in which persons are treated, or treat others differently because they have a specific genetic condition that causes or may increase the risk of an inherited disorder. In the latter instance, both direct and indirect discrimination are a possibility. In the case of indirect discrimination, this could be based on notions of race, sex or ethnic origin, as some genetic anomalies are regarded as particular to certain ethnic or racial groups or to the sexes. For example, sickle cell anaemia is mainly found in individuals of African descent, Tay-Sachs disease in Ashkenazi Jews, whereas cystic fibrosis is (incorrectly) perceived to be more prevalent in persons of European descent. As genomic studies have shown, our perceptions of absolute boundaries between ethnic groups or sex, based on exterior observations, are erroneous. It is genetic links that provide the similarities but of course these are not visible externally.

The South African Constitution provides in section 9 that everyone is equal before the law and has the right to equal protection and benefit of the law, whereas ss 9(3) and 9(4) prohibit direct or indirect discrimination on one or more grounds, some of which are listed (not a closed category). In addition, the Promotion of Equality and Prevention of Unfair Discrimination Act *(No 4 of 2000)* gives effect to the constitutional provision on equality. A person diagnosed with a genetic disease which severely impacts on his or her life, would arguably suffer from a 'disability'. Discrimination on such grounds will be presumed to be unfair, unless the presumption can be rebutted by the person against whom the allegation is made.

Data privacy protection laws are important to ensure that personal information, such as genetic and genomic information, is sufficiently protected. In South Africa, the privacy of data and access to data are regulated by the POPI Act *(No 4 of 2013)* as well as the Promotion of Access to Information Act *(No 2*

*of 2000)*. The latter gives effect to a person's constitutional right to access to any information held by the State or any person, required for the exercise or protection of the individual's constitutional rights. The purpose of the POPI Act *(No 4 of 2013)* is mainly to give effect to the constitutional right to privacy, by safeguarding personal information when processed by a "responsible party" and to regulate the manner in which personal information may be lawfully processed in accordance with international standards (s2). Genetic or genomic information would arguably belong to the category of special personal information described in s24(2), which includes amongst others, information relating to the religious or philosophical beliefs, race or ethnic origin, health or sexual behaviour, or biometric information of a data subject. The POPI Act *(No 4 of 2013)* provides for a general prohibition against the processing of special personal information, subject to specific exceptions, for example where the data subject consents to the processing or where this is necessary for historical, statistical or research purposes (subject to further requirement).

The notion of irreversible anonymisation of samples that is undertaken to make it impossible to trace them back to the individual to whom they are related, is not absolute. DNA samples can never really be truly anonymous, a potential consequence of the secondary use of data in genetic and genomic research. On the other hand, from a legal and ethical point of view information that could influence an individual's health or alter the course of a disease should not be withheld. In an under-resourced setting, however, the feeding back of an incidental genomic diagnosis with specific health implications to an individual who does not have access to relevant health care services to treat such a condition further seems unethical. Where possible however, steps could for example be taken around career and family planning. In contrast to the situation where genomic information may have positive health benefits to those who have access to treatment, the same information will not be helpful to those who do not, and may create anxiety and result in social ostracism and stigmatisation and therefore affect their quality of life negatively. The inclusion of a question in the consent form that requires participants to indicate whether they wish to be informed of incidental findings needs to be debated (De Vries *et al.*, 2012a, 2012b).

The CIOMS 2016 guidelines on the ethical criteria on return of results, including incidental findings, propose the following: there must be analytical validity, clinical significance and actionability to qualify for results being returned. This is discussed in section 4.4 (page 62).

Finally, ethical "good practice" requires that research results be communicated back to research participants and their communities. Although often neglected in medical research, there is ample evidence to indicate that research participants expect some form of communication about the research project after it is completed. Care must be taken around the content of such communication, as well as the manner in which it is communicated.

## 4.3 Access to, Use and Re-use of Samples and Data

Achieving a balance between maintaining respect for persons and ensuring that all of humanity benefits from key research findings remains a key imperative in genetics and genomics practice and research. This is particularly true in the era of big data, in which it is recognised that it is not possible to guarantee complete anonymity in perpetuity. This raises important questions related to the use and re-use of samples, storage of and access to samples and data, and consent in the setting of biobanks.

### 4.3.1 Use and Secondary Use of Samples

A key component of genomics and genetics practice involves the storage of samples and data for unspecified future use. As such, genomic practice is closely intertwined with biobanking.

The DoH Guidelines on Ethics in Health Research (2015) advise that careful deliberation is necessary when considering future use of materials. For example, it is accepted now that biological materials cannot be completely anonymised, which means that virtually any sample can be re-identified. Moreover, secondary use of materials or data is possible, which may not always have been foreseen or anticipated at the time of consent. The question arises then as to whether unanticipated research utilising the samples requires new informed consent and, if so, what should be done when a donor is no longer available. The guidelines recommend that, in the absence of broad consent for future use of material or data for research purposes, use of existing or archived material collected for clinical or diagnostic purposes, including waste and surplus samples, requires expedited review. The nature of the previously obtained consent should be determined to ascertain whether subsequent use was envisaged and whether it falls within the scope of the current proposal.

- If so, new consent is not required;
- if the scope of the current proposal is different, then new consent may be required;
- if samples are anonymous and the results of research would not place any individual, family or community at social, psychological, legal or economic risk of harm, then new consent is not required;
- if the link to identifiers exists but is not provided to the research team and the results of research will not place any individual, family or community at social, psychological, legal or economic risk of harm, then new consent is not required;
- furthermore, it is recommended that the person who holds the code or link should sign an explicit written agreement not to release the

identifiers to the research team. This agreement should accompany the submission to the REC. If the samples can be linked to identifiers, the relevant REC must decide on a case-by-case basis whether expedited or full review is necessary.

### 4.3.2 Storage and Sharing of Resources and Open Access Data

Sharing results produced by research is consistently required in many international ethics guidelines, with wording that makes sharing an obligation (Lévesque *et al.,* 2011). However, there is no consensus on the modalities of this ethical duty, i.e. how and when and with whom sharing must take place. Genomic research generates large datasets of genomic and health information that are deposited into centralised databases for large-scale sharing with the broad biomedical research community. Genomics research is therefore dependent on the sharing of data and samples through global collaborative research networks, sequence reference libraries and repositories (Kaye, 2012). To obtain the necessary sample sizes, researchers have developed new models of open access and data sharing, which has the potential to sever the ties between the researcher responsible for participant enrolment and the individual participants in an original study.

It is possible to conduct high-throughput, cost-effective genome-wide association studies in large numbers of individuals with detailed information on phenotypic traits and environmental exposures (The GAIN Collaborative Research Group, 2007). Common methods across such studies have resulted in the formation of networks of genome-wide association studies involving multiple phenotypes. Extensive data sharing facilitates replication of initial findings, but access to large databases carries responsibilities in terms of protecting the confidentiality and respecting the informed consent of the study participants. Data sharing between different biobanks is necessary in order to achieve sufficient statistical power to underpin significant results (Harris *et al*., 2012).

Access to genotype-phenotype and pedigree data needs to be controlled carefully to prevent identification of individuals or families (Wright *et al.,* 2013). This is particularly the case in Africa, where many researchers and their patients are inexperienced in ethics issues of whole genome and exome sequencing research (WGES). Wright *et al.* (2013) studied the implications of the anticipated surge of next-generation sequencing data in Africa and data sharing concepts on the protection of privacy of research participants. It is essential to perform WGES studies in African populations to ensure that the benefits of genomic medicine are available to all global populations, but it will be equally essential to develop local policies and legislation relevant to WGES research (e.g. informed consent, data sharing, and the return of results) for performing successful genomics research in Africa. The authors conclude that novel approaches to informed consent will help to avoid compromising the privacy of individual participants.

Robinson *et al.* (2013) looked at the question of whether subjective understanding and comfort with decision-making are sufficient to satisfy the ethical principle of respect for persons. They conducted a study with experimental informed consent documents with participants being recruited to genomic research studies, and found that many participants were not completely aware that they were participating in a genomic research study or what that participation entailed. This poor recall of study participation and understanding of who could access and use their genetic information did not impact participants' final data sharing decisions or their willingness to participate. They were comfortable with their data sharing decisions, despite not having thoroughly considered the implications or risks involved. Most of the participants expressed a high degree of trust in the researchers. Participants expressed a desire to be involved in the decision about data sharing. They felt that the best way to respect research participants was to be transparent, provide them with information, and offer them choices.

Knoppers *et al.* (2014) proposed that an international code of conduct be formulated to enable global genomic and clinical data sharing for biomedical research, positioned within a human rights framework. According to the authors, privacy concerns can be attenuated by human rights protections and robust safeguards within a governance model and a code of conduct, to share sensitive data within strict limits that respect both laws and ethics guidelines.

The right of withdrawal is a foundational principle of medical research ethics, and it also applies to the data samples that an individual may have given consent to use in research (Kaye, 2012). In the case of international data sharing it is extremely difficult, if not impossible, to achieve withdrawal when data and samples are shared widely. Increased data sharing impacts on participant confidentiality. Exome sequencing reveals rare alleles, and once a person is re-identified, there is potential for further personal information to be revealed about the formerly anonymous source.

There is a tension between serving individual autonomy interests by keeping data confidential on the one hand, and advancing public beneficence by sharing data liberally on the other (Mathews and Jamal, 2014). Seeing privacy as informational secrecy lends itself to a view of genomic information sharing as a false dichotomy, in which information is either wholly private or wholly public. Current policy restricting access to data as a form of privacy protection both fails to respect those participants who would wish to share their data freely, and limits the potential benefit to science and society from the use of those data. The debate is often framed as privacy *versus* public beneficence and equates respect for persons with informed consent. The authors argue that such norms and practices impede meaningful reform of human participant protections.

McGuire *et al. (*2011) have argued that all data sharing decisions involve an unavoidable trade-off between protecting privacy and advancing research. A major policy concern is that giving participants control over decisions about

data sharing will lead to excessive anxiety about protecting privacy and a reluctance to share data, negatively impacting on research. Data sharing policies must therefore balance the scientific benefits with ethical obligations to participants. A study of different consent types was conducted, in which participants generally accepted broad, but controlled data sharing. The results suggest discordance between existing data sharing policies and participants' judgments and desires.

The internet and social media have changed the landscape of privacy and confidentiality of personal data. Today, empowerment of individuals goes beyond strategies for including the public (Knoppers and Chadwick, 2015). The mechanisms of public engagement have undergone a series of transformations, and within the dimension of citizenry, patients/participants network to make research their own. There is a willingness to publicly share personal and genetic health data on the internet, or to be contacted by researchers for possible inclusion in trials. Today's internet is full of user-volunteered, identifiable data (Mathews and Jamal, 2014). These new realities suggest it is time to revise the ethical relationship between donors and users of genomic research data. The use of social media has resulted in a change in the relationship between individuals and their personal data, enabling increased individual control over how and how much personal data is used in research. Conceptions of privacy and risks of breaching confidentiality are changing rapidly with the ability of IT and social media to change how genomic and other health data are shared and interpreted. Participant-centred initiatives use social media technologies to provide the basis for long-term interactive partnerships (Kaye *et al.,* 2012). Social media technologies are one way of providing a flexible method to give participants different degrees of control according to personal preferences without placing a burden on each participant.

### 4.3.3 Biobanks and Consent to Storage

The open-ended nature of biobanks raises unique challenges for informed consent. Contrary to conventional research where the research is carried out by one researcher or a research team, and where samples are collected for a specific purpose with the informed consent of a participant, samples in a biobank may be used by different researchers for many research projects involving a range of research activities, many of which may not have been foreseen at the time of sample collection (Dhai and Mahomed, 2013). Classical research ethics paradigms relating to informed consent may no longer be appropriate and feasible in the context of biobank research, where a gap arises between the sample collection process and the actual research on the sample, possibly conducted years later and involving research questions and methods that may not have existed or have been considered at the time informed consent was obtained.

Further concerns that arise are those relating to the adequacy or completeness of the information provided; the necessity of new individual consent for each

new use of the sample or data; and whether consent can be regarded as 'informed' (e.g. it would amount to no more than permission), as it may not be possible for sample donors to make informed choices about risks and benefits for unspecified future research, amongst others.

## 4.4 Return of Incidental Findings

The final challenge to seeking consent for genetic and genomic practice – whether for research or for clinical tests – relates to the possibility of uncovering unexpected and unsolicited information that may be indicative of future health challenges. Called 'incidental' findings, such findings can be deeply disturbing to individuals and may cause psychological upset. On the other hand, they may empower individuals to undertake action that prevents or delays disease development, and as such empowers them. The important question with regard to informed consent is whether and how much people should be told about the possibility of incidental findings arising from their involvement in research or clinical testing.

It is essential that patients or participants are informed of possible incidental findings (an updated list) and given a choice about whether and which incidental findings they wish to be informed about, particularly where results relate to conditions that are not life-threatening (Eckstein *et al.,* 2014). The suggestion is that patients and participants should be informed of the possibility that a whole-genome test (whether for personal, clinical or research purposes) may reveal results that are of clinical or lifestyle importance during the consent process. In addition, researchers or clinicians should describe what they will do in that case, and ideally gauge the patient's or participant's desire to receive such findings. Considering that participants and patients also have a right not to (want to) know (Culver *et al.,* 2013; Cowley, 2016), they should receive counselling prior to a test being ordered so that they can indicate which kinds of findings they would like to receive and which they would not – and this should be standard practice before whole genome tests are ordered in the clinical setting. There are several important challenges to consider in this approach. First, consent processes – whether for clinical interventions or for research purposes – are already overburdened and frequently poorly understood. To add an additional level of detail and complexity to these processes is problematic because it does not promote good decision-making. Second, the real challenge in communicating these unsolicited results is that they are potentially numerous and inherently unknowable: not only do we have no way of predicting the kind of findings that may be generated, but neither do we necessarily know how such results may affect the individual or their care. In essence then, talking about these kinds of possible findings is communicating uncertainty. The CIOMS guiding principles for results to qualify for being returned are: there must be analytical validity, clinical significance and actionability.

The situation in the case of paediatric biobanks is different to participant autonomy in adults, because vulnerability in children is linked to their lack of autonomy (Hens *et al.*, 2011). This is one area in which others can take the decision to return findings about early-onset treatable or preventable diseases, even against the parents' wishes. A parent does not have the right of opting out of receiving such information about their child.

In the field of forensics, incidental findings are common. For example, if profiles are compared within a family, a non-paternity may be discovered. Currently, this incidental finding is not communicated to the family, as it is outside the scope of practice of a forensic laboratory.

## 4.5 Consent in the Forensic Context

In the criminal justice system, the Forensic DNA Regulations of 2015, flowing from the Criminal Law (Forensic Procedures) Amendment Act *(No 37 of 2013)* reflects clear stipulations with regard to consent. However, after acquittal or exclusion from a criminal case, the arrested person has the right to request the removal of their DNA profile from the NFDD of South Africa. Again, this poses at least two challenges that may be mutually exclusive: (a) the person may not be aware of this right, and although ignorance of the law is not legally accepted as an excuse, one has to take the societal level of DNA awareness into account; at the least an arrested person should be made aware of this right; and (b) the primary criminal matter may be completed, yet if the profile is permanently removed from the database, it precludes any future matches, as well as exclusions, from criminal investigations. It is evident that these aspects require informed debate at the national level, including the involvement of civil society organisations and/or representative groups. Section 12 of the Regulations stipulates the process for "removal of forensic DNA profiles from the NFDD on application": such removals must be executed within 30 days after receiving the relevant notifications. It is not evident that this timeframe is realistic and previously validated data should be used to revisit this timeframe.

## 4.6 Discrimination and Stigmatisation

Despite the benefits to humankind that are unlocked by advances in modern genetics, intricate ethical, legal and social questions arise that are rooted in issues of privacy and confidentiality (Watson, 2000; Slabbert, 2007; Slabbert, 2008). The disclosure and use of genetic and genomic information may not only lead to the stigmatisation of an individual or certain groups, but may have other legal ramifications in the contexts of finance, education and employment (Rothstein, 1990; Kupfer, 1993; Rothstein, 1997). Internationally, a number of hard and soft instruments have been developed to deal with the risk of genetic discrimination, particularly in relation to the use of genetic information as a basis for excluding individuals from purchasing health or life insurance (Joly *et al.*, 2017).

Genetic discrimination has become the focus of human rights protection through the inclusion of specific provisions in a number of key international instruments, requiring states to protect citizens against genetic discrimination. Most notably is the Universal Declaration on the Human Genome and Human Rights (1997) from the United Nations Educational, Scientific and Cultural Organisation (UNESCO) which provides in article 6 that "[n]o one should be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity". This was followed by the UNESCO International Declaration on Human Data (2003), prohibiting discrimination and stigmatisation in article 7: "[e]very effort should be made to ensure that human genetic data are not used for purposes that are discriminatory or in any way that would lead to the stigmatisation of an individual, a family or a group". The same declaration provides for restriction on the disclosure of genetic data to third parties, specifically insurers and employers. These instruments are important normative statements that guide the establishment of international standards, albeit lacking legal force.

At the supranational level, the Council of Europe's European Convention on Human Rights and Biomedicine (1997) prohibits any form of discrimination on the grounds of a person's genetic heritage in article 11. Similarly, the European Union's Charter of Fundamental rights, enacted in 2000, contains a non-discrimination provision relating to genetic characteristics (article 21).

In South African law, the right to equality and equal protection and benefit of the law is protected in section 9 of the Bill of Rights (South African Constitution). The same section provides that neither the 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 may include a diagnosis of or predisposition to a genetic disorder, is however not mentioned in section 9, but may arguably be included under "disability". In the case of Hoffmann v South African Airways (2000) the right to equality on an unlisted ground (e.g. HIV-positive status) was addressed. The Constitutional Court held that HIV was not a "disability," but found nonetheless that discrimination on this basis would constitute an infringement of dignity, as it was discrimination based on a person's medical health. By analogy, unfair discrimination on the basis of a person's genetic profile would be unconstitutional. Discrimination on the grounds of race or ethnic origin is also possible, as certain genetic disorders pertain specifically to certain ethnic groups. Unfair discrimination is furthermore comprehensively regulated by the Promotion of Equality and Prevention of Unfair Discrimination Act *(No 4 of 2000)*.

One risk related to the involvement of population groups in genomics research is that research results could contribute to existing stigma for those groups, particularly where genomics research involves stigmatised conditions or where

the groups are already politically, socially or economically marginalised (De Vries *et al.,* 2012a; 2012b). While the likelihood of genomics research causing stigma where none existed is questionable, there is some evidence that genetic attribution could affect stigma associated with disease, either by increasing it as was reported in the case of podoconiosis genomic research in Ethiopia (Tekola *et al.,* 2009), or by reducing aspects of disease-related stigma as may be the case for deafness (Sankar *et al.*, 2006) and mental illness (Phelan *et al.*, 2002; Link *et al.*, 2004; Phelan *et al.,* 2006). Evidence that genetic attribution could increase stigma for population groups is ambivalent: while there are well-reported instances of genomics research increasing group-stigma for clearly identifiable ethnic groups, such as the Havasupai (McGregor,2010; Mello and Wolf, 2010) and religious groups such as the Ashkenazi Jewish population (Raz and Vizner 2008), early evidence that genomic research on the southern African Lemba tribe confirmed traditional narratives of Jewish descent empowered this group and possibly reduced stigma (Parfitt, 2003; Parfitt and Egorova, 2006) counters this evidence.

While questions about the effect of genomic research persist, there are some general best practice guidelines that can be drawn. These are that a) in the case of working with small, identifiable groups that are already socially or politically marginalised, researchers should take extra care not to publish research results that could be perceived to be stigmatising by the groups or others; b) the same is true when working on conditions or attributes that are known to be stigmatised, such as for instance some mental illnesses, addiction, or sexual orientation. Where genomics research is conducted on groups that are thus vulnerable, it is imperative that researchers conduct extensive community engagement to ensure that the groups understand and support the research that is being done; that researchers understand the nature of existing stigma and how their research can impact on it; and that an opportunity is created for researchers and community members to agree on the best way to describe their group in publications emanating from the research. In this case, there should ideally also be an opportunity for researchers to discuss findings and publications with community members before the results are published, to ensure that they are appropriately interpreted and contextualised, and that the possibility of increasing stigma is reduced.

South African law comprehensively protects against unfair discrimination, which includes unfair discrimination on the ground of a person's health status, which may include suffering from a genetic disorder, as argued above. Discrimination and stigmatisation go hand in hand, as stigmatisation is most often both the cause and result of unfair discrimination. Increased public awareness of the legal framework protecting against unfair discrimination, and specifically protection against unfair genetic discrimination in the context of health care, insurance, employment and education, may assist in emphasising the rights of persons not to be subjected to unfair discrimination (and stigmatisation) on the basis of a genetic condition or disorder.

## 4.7 Recommendations – Respect for Persons

### R5. Ubuntu philosophy

a) The Ubuntu principle must be promoted in genetics and genomics research, health care delivery and forensics practice.

b) Recognition must be given to the fact that while the concepts of autonomy and Ubuntu may be in tension, these are complementary rather than mutually exclusive principles and that all fundamental rights should be understood within the matrix of the community. Relative solidarity is an important component of Ubuntu.

### R6. Consent models for genetics and genomics work

a) Empirical research should be conducted to establish South African participant views on consent models.

b) It must be recognised that blanket consent is incompatible with South African legislation (e.g. The POPI Act *(No 4 of 2013)*.

c) The NHREC should be encouraged to prepare an informed consent template for genetics and genomics. The informed consent template should include the following considerations: whether results will be returned; benefit sharing arrangements; sample and data storage and re-use, including governance thereof; limits to the withdrawal of samples and data once shared; details regarding export of samples; privacy protection in countries to which data and samples are exported; and the specific circumstances that limit confidentiality related to DNA data.

d) The DoH Guidelines on Ethics in Health Research (2015) that permit broad, tiered and specific consent models should be fully implemented. The panel recognises however that there is lack of consensus regarding the impact of the POPI Act *(No 4 of 2013)* on broad consent, and that the situation may change once clarity is obtained from the Regulator.

### R7. Protection of information and resources

a) Oversight provided by RECs on future use of genetic material (samples and data) must ensure that proposals indicate whether storage is desired and if so, informed consent documents must include the relevant information to permit a voluntary informed choice by participants.

b) Researchers should not report their research findings in ways that may be, or may be perceived to be, harmful or offensive.

c) Engagement with the Information Regulator, Department of Justice, is important to discuss the development of regulations in the POPI Act *(No 4 of 2013)* and how this will impact on genetics and genomics research.

d) A policy should be put in place to guide decisions about the disclosure of incidental findings.

e) The challenges related to the timeframe of 30 days to remove a DNA profile from the NFDD should be revisited.

f) The establishment of a SAHGAB should trigger discussions with civil society with regard to the implications of forensic practices related to genetics and genomics, including the NFDD.

### R8. Communities, families and vulnerable and marginalised individuals

a) When working with small, identifiable groups that may already be socially or politically marginalised, researchers must include in the community engagement process a discussion on the manner in which the research process and outcomes will be managed to mitigate potential harm to the community, e.g. unintended perceptions of stigma.

b) Researchers investigating certain conditions, phenotypes or behaviours must also include in the community engagement process a discussion on the manner in which the research process and outcomes will be managed to mitigate potential harm to the community.

# 5 Good Stewardship

Good stewardship denotes careful and responsible management of resources that are entrusted to one's care (World Conferences on Research Integrity Foundation, 2010). In genomic research, good stewardship could be understood as "the responsibility for the sustainable and careful use of genomic resources, reflected as both a value and practice by individuals, communities, organisations, companies and governmental institutions" (adapted from International Organisation for Standardisation (ISO) 20121, 2012). 'Good stewardship' is intended to emphasise the inherent characteristics of integrity, honesty, collegiality, accountability and sharing that make up the notion of stewardship. Stewardship is the process of acting in a 'care-taking' role on behalf of for example, society in terms of genomics and genetics. As far as genomics and genetics are concerned, it is implied that subject matter knowledge is required in order to act as a steward. It is therefore the professional's role in this field to act as a steward in the interest of the rest of the people of South Africa, since they have the subject matter knowledge and expertise. This role should be exercised without fear or favour and should be done objectively, with the benefit of society as goal.

A widely-held view is that genomic resources should be viewed as a common good, which implies that use or possession should not lead to monetary or other gain for individuals. In a similar vein, research data or innovations generated by studying or working with the human genome should benefit all humans, i.e. the global population, and especially the population of the country that provides the samples and data. As will be explained below, South Africans are sceptical about individuals obtaining exclusive rights and potential monetary gains out of samples and data provided in the context of research or clinical care. Obviously, however, a genomics project cannot be sustainable in the absence of funding. Equally obviously, some monetary gain is inevitable given the prevailing proprietary system, which recognises intellectual and other property rights, and which applies also to genetics and genomics in South Africa.

The Universal Declaration of Human Rights contains complementary rights *viz.* to share in scientific advancement and its benefits, and authorship protection of moral and material interests that result from scientific production (UN General Assembly, 1948). These rights have been applied to genomics research; they offer some protection for both sample donors and researchers involved in the research.

## 5.1 Accountability and Sharing

A good governance framework for genomics work in South Africa should promote accountability and sharing by requiring evidence of 'social value'

to prevent unfair exploitation of those who provide biological samples. Thus, promoters of an initiative must demonstrate that South African society, as a whole, would benefit from the research and not just particular individuals, companies or foreign collaborators.

With regard to international collaborative research, accountability and sharing require a governance framework that takes into account local needs of the provider and the recipient. The complexity of these relationships has prompted the creation of entities, such as the Council on Health Research for Development (COHRED). The Research Fairness Initiative developed by COHRED aims "to create a reporting system that encourages governments, national research and innovation agencies, academic and research institutions/organisations, business, organisations and funders to describe how they take measures to create trusting, lasting, transparent and effective partnerships in research and innovation". A second important resource is the Accountability Policy of the Global Alliance for Genomics and Health.

While most agreements about the re-use of genomic resources rely on goodwill and responsible conduct, an important component of ensuring accountability is nevertheless that there are real repercussions for non-compliance (Shabani *et al.,* 2016). Joly *et al.,* (2011) outline a number of concrete sanctions that could be used if people violate the terms of data access and re-use. Joly *et al.* (2011) outline 'community-based' sanctions governed by scientists. Sanctions in this realm range from withdrawing access privileges and requesting the destruction of any resources held locally, to alerting journal editors and funders of data breaches. Legal sanctions include fines and prison sentences, but these seem to be less common in regulating the re-use of genomic resources. Joly *et al.* (2011) point out that it is very important that the limits to agreed resource re-use are transparent and clearly spelled out so that there is no ambiguity in determining what is and what isn't permissible regrading re-use of samples and data. The Accountability Policy of the Global Alliance for Genomics and Health offers procedural guidance for the incorporation of accountability into data and sample sharing policies.

### 5.1.1 Accountability

Accountability throughout the research process, beginning with sample collection and management, but also in relation to the secondary use of samples and data can inspire trust for users, donors, and other interested parties. Fears borne of suspicion and misperception may be allayed by clear descriptions of the project, how it works and how ordinary people are also involved. Such descriptions should also outline the nature of conduct that would be considered trustworthy. Taken together, such descriptions form a so-called 'governance framework', the overall goal of which is to ensure that genomic resources are managed carefully, responsibly and sustainably in a manner consistent with stewardship obligations. Core features of a trusted framework are transparency of expectations and processes, as well as consistency in carrying out requirements.

A good governance framework for genomics work must require descriptions in research proposals and collaboration agreements that articulate the nature of the benefits likely to accrue from the genomics research initiative and how the benefits would be shared with relevant stakeholders. Key is that funds must be available to ensure that benefits are delivered, e.g. if capacity development is the benefit, it is unlikely to be sustainable or meaningful if not accompanied by financial resources, a training plan, and long-term career mentoring.

Practitioners in the fields of genomics and genetics should be held to high standards aligned with the appropriate ethics standards of their professions. If discipline-specific ethics standards do not exist, they should be drafted so that practitioners may be held accountable via appropriate and legally mandated structures. This is also required for the medical and natural sciences that overlap with the fields of genetics and genomics, e.g. forensic science. With regard to forensic science, it is important to update the legal frameworks and Acts regularly to stay aligned with new developments and technologies in the field.

Good stewardship implies a gate-keeping role for those who are duly qualified and certified to work in genetics and genomics. Practitioners who practise outside their fields of expertise may conduct themselves unethically insofar as their lack of appropriate expertise may not serve the needs of civil society.

### 5.1.2 Sharing

Genomics work, whether for clinical, research or forensic needs, occurs in a context of re-use of samples or data by people not originally involved in their collection. Sharing of data is inherent to genomic work (large numbers of participants and large datasets are required for meaningful outcomes) and have become commonplace, with research collaborations developing resource-sharing policies that describe the responsibilities, the means and the conditions of sharing (World Conferences on Research Integrity Foundation, 2013; 2017). Where only data are to be shared, the policies are called Data Sharing/Release Access Policies. When samples are shared, they are generally called Sample Sharing/Release Access Policies and a Data and Biospecimen Sharing/Release Access Policy describes the situation where both data and samples are shared. Many international collaborations have developed such policies, with multiple examples being available online to help researchers customise for own use. The governance framework developed by the Human Heredity and Health in Africa (H3Africa) Consortium has both sample and data release policies that include particular features of the African research and health care context essential for developing fair and equitable access that promotes African genomics research (De Vries *et al.*, 2015). These policies already govern many of South Africa's data and sample collections.

A critical issue for sharing of genomic samples and data is when resources for secondary use should be made available. Several international policies advocate for data release immediately after curation, while others recognise

that this approach disadvantages researchers in LMICs (Bull *et al.,* 2015). In the case of samples, no uniform release policy exists and guidelines in this regard would be beneficial to the South African national research agenda.

Various mechanisms are employed to ensure that researchers in LMICs have a fair opportunity to use genomic resources meaningfully (Bull *et al.,* 2015; De Vries *et al.,* 2015).

a) One mechanism is to impose an absolute embargo that delays release of resources for a reasonable period to allow sufficient time for researchers to work with samples, analyse data and submit manuscripts for publication.

b) A second mechanism uses a conditional embargo that permits sharing but restricts the topics of research open to researchers outside of LMICs. The LMIC-based primary investigators outline the research questions that they will pursue within a stated time frame. Other investigators may not publish on the selected topics during an embargo period.

c) A third mechanism outlines specific additional requirements for secondary use, such as meaningful capacity building and involvement of LMIC-based researchers.

Initiatives can blend these strategies, for instance requiring that proposals for secondary use includes meaningful ways of building South African research capacity.

Sharing mostly involves genomic and phenotype data generated in the course of research, even where original samples were collected for clinical or forensic reasons. In addition, sharing may involve DNA samples for re-use. The chance of discovering new scientific knowledge is increased by sharing samples and data for re-use. In turn, sharing increases the scientific utility of genomic resources as large numbers of participants with phenotype and genotype data are required to render datasets useful. Sharing promotes operational efficiencies by reducing costs by avoiding repetitive sample collection and by reducing the burden on participants/patients or other volunteers by diminishing the number of contacts and consent-taking events. Sharing may also help to promote fairness amongst researchers by allowing access to and use of resources, rather than concentrating funding and research work in a limited number of well-resourced laboratories and research teams.

On the other hand, sharing genomic resources raises concerns about protection of donors' privacy and the possibility of harm to donors. Some concerns flow from socio-political perceptions and views about historical imbalances in power relations due to racist policies, in terms of which respect for persons was lacking. Article 9 of the UNESCO Universal Declaration on Bioethics and Human Rights states that "the privacy of persons concerned and 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, particularly international human rights law". South Africa's POPI Act *(No 4 of 2013)* gives effect to Article 9. Although ethics guidelines that govern research cover this aspect, the risks related to digital storage of information should not be underestimated.

Sample and data access decisions must be regulated by dedicated committees that review access requests. Access committees should include members with varied expertise relevant to genomics research or biobanking, including legal experts, scientists, bioinformaticians and ethicists. To ensure that access decisions are appropriate, it is important that members of such committees are knowledgeable about the context within which research samples and data were collected, and to which research results pertain. Where genomic samples or data pertain to South Africans, the access committee must include South Africans.

### 5.1.3 The Role of Communities

The role of communities in genomic stewardship, particularly in relation to downstream governance of sample and data access and re-use is important. The notion of 'community' (See 3.2, page 30) should be explained in governance documents since a variety of meanings of the term prevail in South Africa. Some people understand the term to describe people in a territorially-defined area, while other meanings include particular social groups, laypersons, advocacy groups, interest groups, or people defined by specific diseases or conditions. In the genomics context, a useful approach is to encourage a broad understanding of 'community' as in 'ordinary people', since genomics work should aim to benefit everyone.

While, necessarily, experts would set up the framework and operational requirements for sample and data collection, storage, access and re-use procedures, the involvement of ordinary people is vital to allay negative perceptions and fears of having poorly understood procedures imposed on them. In addition to the technological and scientific developments that may pose difficulties for lay persons' understanding, there is significant concern about information that indicates or creates the perception that use of samples or data leads to wealth-related ends, even if a health-related outcome is achieved at the same time. Perceptions prevail that it is unfair to expect ordinary people to provide their biological samples and data for free, while others benefit downstream. Usually much of the financial support for a (national) genomics project emanates from State coffers, which acquires its funds from tax collection. This means that ordinary people contribute to the financial sustainability of the project, which gives them a vested interest in knowing how their taxes are spent. Whether individual reimbursement is possible, or whether a system of more general benefit sharing may satisfy, must be addressed transparently and

reasonably through engagement with ordinary people across the country. The goal of engagement is to achieve broad understanding amongst communities of the reasons for genome work, the anticipated benefits (at least for future health care improvements and disease prevention), as well as the precautions exercised to avoid harms and wastage.

Before national and publicly funded projects get underway, public engagement is essential. The purpose is to communicate and engage on the anticipated benefits and the uncertainties involved; to ensure that transparency, fairness and mutually accepted appropriate processes are present; and to ensure that voices from all parts of the community are heard and considered.

To engage with a community only before a project begins is insufficient; on-going communication and genuine involvement is important for perceptions of sincere respectfulness to prevail. Opportunities must be explored to involve communities in decision-making about access and re-use of data, even when the decisions are made many years after the collection of samples. Various models of community involvement have been suggested, e.g. a charitable tissue trust that includes long-term community involvement. The South African context could use a similar non-profit legal entity model. Decision-making would be informed by ongoing community engagement about identifying on-going sample and data use, and potential restrictions to sample and data use that may be required. The tissue trust model proposes that secondary samples and data use should be subject to a fee, which could be used to strengthen community development, community health and research literacy. It could also lead to the development of scientific and other research-related infrastructure and capacity building so that, over time, genomics projects can be initiated by South Africans with significant input from ordinary people.

Another framework model is the 'DNA on Loan' model developed by Canadian aboriginal people and genomics research communities in Canada (Arbour and Cook, 2006). Acknowledgement of the sacredness and deep religious significance of biological material to aboriginal Canadians is reflected in the arrangement whereby the samples are given in trust (or lent) to genomics researchers for specific projects. Phased consent procedures permit the donors to retain control over the use and re-use of their samples and data. If researchers want to conduct additional research, or make samples available for use by researchers not involved in the original project, application is made to the communities which decide whether to permit further use and on the appropriateness of re-use. The character of this model resonates in the South African context where similar views prevail about human biological material and data.

## 5.2 Governance of Genetic and Genomic Resources

An appropriate governance framework for genomics resources should outline the policies (data and sample sharing, including who may access and use

resources, the scope of use permitted, expectations for evidence of benefit sharing, and requirements for payment of costs); regulatory matters (material and data access agreements); as well as the entities (e.g. gatekeepers) that deal with applications to access and use genomic resources. A fundamental assumption for the framework is that governance processes and procedures are infused with integrity, honesty, responsibility, accountability and efficiency.

The design of the framework should articulate the essential ethical values of genomics work (fairness, equity, protection of donor interests) and explain how these values are promoted. The ethical principles that underpin genomic clinical and research work must also be evident. The highest ethical and regulatory standards are required for both clinical and research contexts.

The tenor of the framework should be proactive rather than reactive. While procedures and sanctions for managing misconduct are necessary, the emphasis should be on training in governance, ethics education that promotes ethical conduct and facilitates a healthy clinical and a research environment free of fear, bias, undue influence and corruption. South African researchers should be empowered to engage comprehensively, meaningfully and equitably in genomics research, so that outcomes lead to optimal benefits for South Africans.

### 5.2.1 Applications of Genetic Testing

In recent years, there has been a proliferation of genetic and genomic testing and the use of molecular technologies to investigate genomics and genetics in allied fields. Examples include the emergence of nutrigenomics (genetic tests to guide nutritional choices), wellness tests (using a limited number of genetic markers of questionable relevance to health) and sports performance genetic tests that are recommended by dieticians, biokineticists and others. There is concern that these practitioners have not received appropriate training in genetics or genetic counselling and are not appropriately registered for this purpose. A second concern is a lack of transparency with regard to the scientific accuracy and utility of the tests that are being offered, and that the laboratories and their staff are not appropriately trained or experienced (or registered with a professional body) in the accurate interpretation of the tests. In addition, they have not been trained in delivering the test results and dealing with the outcomes. Such practices are in contravention of the Health Professionals Act *(No 56 of 1974)*. The provisions of the Act are designed to protect health care users and health care providers.

In South Africa there is currently no process that assesses and regulates the introduction and application of genetics tests. The Medicines and Related Substances Act *(No 101 of 1965)* and subsequent modifications to the Act, govern the activities of the Medicines Control Council of South Africa. The Medicines and Related Substances Amendment Act *(No 72 of 2008)* describes the establishment of SAHPRA that is extending the Act's mandate to include medical devices. Medical devices include diagnostic tests and would therefore

also cover genetic tests. The committees and processes of SAHPRA are in the process of being developed and there should be active engagement from the genetics community to develop a strong regulatory framework for genetic tests and to establish guidelines for quality assurance in genetic laboratories.

It is imperative that the diagnostic validity and standards for genetic tests that are being offered to patients in South Africa be appropriate. Currently, medical insurance companies decide on the appropriateness of particular tests vis-à-vis other tests, but the decision-making process is opaque and it is not clear which considerations are made to determine which tests will be offered. A further concern is that the contracts between medical insurance companies and the companies producing genetic tests are not open to public scrutiny. In addition, the evidence base for the applicability of international tests in the South African population is often lacking. There is anecdotal information that this state of affairs has led to the continued use of genetic tests used in other parts of the world that are blacklisted in South Africa.

Genetic testing is also performed in the field of forensics. This includes applications of individual identity in criminal cases, family relationships in immigration disputes, parentage testing and identification in mass disasters. Forensic testing therefore requires similar legal and regulatory frameworks to ensure quality testing and reporting. Forensic science is currently an unregulated profession in South Africa; efforts to ameliorate this situation are however underway. SACNASP is mandated to develop regulations for the forensic science profession (Natural Scientific Professions Act).

#### 5.2.1.1 Validation of Genetic Tests

All genetic tests need to adhere to strict regulations and standards of scientific and analytical validity (Organisation for Economic Co-operation and Development (OECD) Guidelines for Quality Assurance in Molecular Genetic Testing, 2007). In a resource-poor setting like South Africa, it is also important to consider clinical utility in a medical setting and accessibility in the public sector. Tests offered to the public should have a sound scientific basis and be validated for use in specific ethnic groups. All diagnostic tests should be peer-reviewed, evidence-based and appropriate, as prescribed by ISO 17025:2017. This ISO standard addresses the issue of "impartiality" that is viewed equal to the following terms: "freedom from conflict of interests, freedom from bias, lack of prejudice, neutrality, fairness, open-mindedness, even-handedness, detachment and balance" (ISO 17025, 2017). This is not only in line with the scientific method, but it is also aligned with public interest. The above not only holds true for diagnostic testing, but is equally true for DNA testing in the forensic context.

#### 5.2.1.2 Accreditation of Genetic Testing Laboratories

Laboratories providing genetic and genomic testing should be accredited by the South African National Accreditation System (SANAS), the body that

is legally mandated to accredit laboratories in South Africa according to the Accreditation for Conformity Assessment, Calibration and Good Laboratory Practice Act *(No 19 of 2006)*. Accreditation of laboratories in general is not currently a legal requirement, and there are still laboratories in South Africa that offer genetic tests and services without accreditation. However, in the forensic science sector it is a legal requirement (See below). Although accreditation is not a guarantee of quality, at the minimum it assures the user of compliance with minimum standards of quality assurance at all levels of laboratory management.

The National Forensic Science Laboratory is not yet SANAS-accredited. This is not in line with global practice where national laboratories are legally mandated to be accredited. In South Africa both the South African Police Service Act *(No 68 of 1995)* and the Forensic DNA Regulations (2015) of the Criminal Law (Forensic Procedures) Amendment Act *(No 37 of 2013)* in section 15P require that forensic DNA samples be processed in an accredited laboratory, and that the laboratory comply with the appropriate ISO standard (ISO/IEC 17025 in this case). Although this mandatory requirement is already enshrined in law, it is to date not enforced.

The reasons for accreditation are evident in terms of scientific validity, but at the least, it builds trust between government and the citizens of the Republic it serves. In accredited laboratories, there is regulation of the entire process related to the testing of forensic biological samples. This is currently lacking in the South African context and may hamper the effective delivery of justice which is contrary to the stated NDP goals.

#### 5.2.1.3 Regulation of Genetic Practitioners

In South Africa all health care practitioners are required to be registered with the HPCSA as cited in the Health Professions Act. Each profession has the requirement of stipulated qualifications, structured training and documented experience prior to registration. In the field of genetics, medical geneticists (sometimes referred to as clinical geneticists) require specialisation in medical genetics through The Colleges of Medicine of South Africa and registration with the Medical and Dental (and Medical Science) Board of the HPCSA. The Medical Science Committee of the Medical and Dental Board registers medical scientists in the field of genetics and genetic counsellors. Technologists who practise in the field require registration with the Medical Technology Board of the HPCSA. It is mandatory for genetic practitioners that request and/or perform genetic testing for the purpose of diagnosis or to inform medical treatment, to be registered with the HPCSA.

There are however no structures in place to regulate genetic practitioners who offer genetic tests with no direct clinical benefit and who often have no genetics training. The challenge is that whilst some of these practices fall within the area of expertise of professionals, it is important to determine whether and to what

extent such professionals need to receive training in genetic methods and the interpretation of results to ensure that the feedback they give their clients is accurate, not misleading and free of harm. Similarly, it is important to ensure that the kinds of genetic tests used in this context are appropriate for the South African population and for the conditions being tested. There could be ways to ensure the appropriate use of genetic tests to support professional practice in nutrition, sports performance and other fields. These may include regulation of the tests as medical devices by the newly formed SAHPRA or through other professional organisations, such as the Association for Dietetics in South Africa. The assessment of tests should however be done by trained geneticists rather than fellow dieticians or other practitioners with little or no training in genetics.

### 5.2.2 DNA Storage, Import and Export

Human biological material is inconsistently and confusingly defined and described in the NHA and associated regulations and does not clearly define DNA as a biological material. The lack of clarity makes interpretation of the regulations difficult. For example, the regulations relating to Tissue Banks (2012) define 'tissue' as a "functional group of cells". The term is used collectively in the regulations to indicate both cells and tissue. However, a 'tissue bank' is defined as providing materials for transplant, which restricts the notion of 'tissue' to one area of application and does not include DNA biobanks for the purpose of research or DNA in analytical pathology laboratories.

An authorised institution that keeps genetic material and related records including individually identifiable information or related health information, has to meet several requirements, according to clause 13 of the NHA's regulations relating to the use of human biological material (2012). They must ensure that no disclosure of information occurs without written informed consent that confidentiality is ensured, that written informed consent is provided for long-term storage, and that information to be used in research must be anonymous. The latter requirement may need modification, as it is well known that complete anonymity cannot be guaranteed since each individuals' DNA sequence is unique (with the exception of identical twins, with regard to nuclear DNA). The categorical statement in the regulations relating to stem cell banks (2012) that all data including genetic information are confidential illustrates the need for clear measures on how to handle such data. Valuable genomic resources are generated during routine clinical investigations and the combination of genomic and clinical data from hospitals and other health care facilities has the potential to contribute toward future personalised medicine. Such resources could and should be harnessed for research purposes and the generation of new knowledge with future clinical benefit (Knoppers *et al.,* 2014).

mport and export of human tissue, blood and blood products, cultured cells, stem cells, embryos, foetal tissue, zygotes, and gametes are permitted subject to obtaining the appropriate permits issued by the Director-General of Health (Clause 2 of the NHA's regulations (regulations relating to the import and export

of human tissue, blood, blood products, cultured cells, stem cells, embryos, foetal tissue, zygotes and gametes, 2012). However, contradictory information appears in Clause 4(2) of the same regulations where import and export of placenta tissue, embryonic or foetal tissue, or embryonic, foetal and umbilical stem cells are forbidden unless the Minister gives written permission. Clause 4(10) of the same regulations provides that biological material may be exported only to Southern African Development Community (SADC) countries. The same regulations do not apply this limitation to the import of human biological material, though. This is most astonishing, given the myriad collaborative research studies that currently share biological material and data, as well as the number of samples that are exported for diagnostic purposes to countries that have more advanced technological capacity than South Africa does. The potential for confusion is self-evident.

Experience demonstrates that sharing cannot occur on the basis of good faith alone, as 'misunderstandings' occur which are detrimental to the investigators who built the research resources, as well as for the society from which the samples came. To ensure appropriate use of genomic resources, good practice guidelines recommend that data and material transfer agreements are signed by both the recipient and the donor when resources are shared. Data transfer agreements (DTAs) would, for example, contain clauses related to data ownership, permissible use of the data, how it may be shared (or not) with third parties, how credit should be attributed and how IP would be dealt with should this become an issue. Material transfer agreements (MTAs) are required to promote good governance and are required, together with an ethics approval letter for collection of the samples, by the DoH prior to shipping samples from South Africa.

With regard to storage of DNA reference samples in forensic testing, regulation (10)(1) of the Forensic DNA Regulations (2015) stipulates that buccal samples as well as DNA samples "must be destroyed within 30 days of obtaining a forensic DNA profile or after the sample has been processed by the Forensic Science Laboratory". This principle may not be practical in terms of the requirements of the justice system. Realistic timeframes, based on previously validated data, should be adhered to.

Ultimately, a universal objective of responsible stewardship of genomic resources would be to ensure their contribution to the improved health and well-being of the people most affected by disease. To achieve this in a responsible manner would include appropriate consenting of patients and well-documented storage and sharing policies and practices. It has been argued that we need a new framework to integrate the data-intensive sciences (such as genomics and transcriptomics) with mechanisms to address stakeholder concerns among patients, society and government (Dandara *et al.*, 2012).

### 5.2.3 Biobanks

Biobanks raise pertinent challenges relating to the protection of personal information (e.g. medical records of sample donors). Access to these records should be carefully managed via effective and sound policies or a written authorisation by the participant that would balance the privacy rights of research participants with other competing interests. The right to withdraw samples and information derived from samples is also problematic, as these may already have been extensively distributed, processed, transformed and exchanged across several databases on a global scale. Participants should be informed that the right to withdraw in biobank research is not a straightforward matter.

The current legal position is that no statute or regulation in terms of the NHA specifically addresses storage of DNA or the establishment of biobanks in South Africa. Some evidence of governance provisions for both topics appears in a variety of legal sources. However, the need for clarity in the legislation and regulation to describe a clear legal and ethical framework that is both feasible and pragmatic in the South African context, as well as compliant with international standards, is considerable.

The NHA implies that storage facilities and access thereto are intended because the Act provides for a variety of human biological materials to be collected and used even though it does not include provisions describing where and how storage is to be managed. The regulations issued in terms of s 68(1) of the NHA mention stem cell banks (regulations relating to stem cell banks, 2012) and tissue banks (regulations relating to tissue banks, 2012). By definition, these banks are for therapeutic (transplantation) purposes only; the regulations omit to provide for biobanks. The envisaged governance framework should clearly describe the role and function of biobanks, as well as outline and allocate responsibilities to the relevant role players, and provide procedures to ensure accountability of the role players for the way in which they manage, use and distribute genomic samples and data.

A clear description must be established and circulated widely to standardise understanding and usage. Appropriate biobanks and data repositories must be established and maintained.

There are different types of biobanks that are aligned with their specific purpose, and these are funded and managed in different ways. They include academic research biobanks, public biobanks (e.g. the United Kingdom Biobank) and private biobanks. Academic research biobanks are usually smaller, funded through research grants, managed by institutions of higher learning and approved by institutional ethics committees. Public biobanks are regional or national initiatives, funded by the State through taxpayer contributions, but could involve public-private partnerships. Private biobanks are typically for financial gain. Affordable and sustainable biobanks can be developed in resource-limited settings (Soo *et al*., 2017).

### 5.2.4 Data Management

Rigorous data storage, management and governance processes are essential for responsible curation and use of health-related data, including genetic and genomic data. Data related to the storage and use of biological specimens should be managed with an appropriate electronic laboratory information management system (LIMS) to preserve the integrity of the data. There are many commercial LIMSs, invariably acquired at considerable cost with the need to customise and pay annual licensing fees to companies. There are, however also several excellent open source options, but some may require considerable technical expertise to customise and maintain.

In the forensic context, LIMSs should be linked at the national level to all forensic digital networks to optimise the evidential value that could accrue from these linkages. This would require the harmonisation of data and systems to exchange information. Given that crime knows no borders, links to external systems at the SADC and global level should be sought to maximise the promise of justice to society at large.

The NFDD poses particular challenges related to the justice system. The body that is mandated to oversee the NFDD, the National Forensic Oversight and Ethics Board should be effective and resourced appropriately to fulfil this role.

### 5.2.5 Return of Genetic Results to an Individual or Family

One of the most pertinent ethical challenges in genomics care and research relates to whether, when and which genetic results ought to be fed back to patients or research participants. In section 3.1 some considerations about the consent process in relation to incidental findings are detailed and this issue in relation to governance is addressed. The ongoing development of genomic tools has led to a significant decrease in the cost of running large diagnostic and research platforms resulting in the generation of a large volume of data for each individual, including potentially important clinical information about susceptibility to selected conditions that were not originally screened for (in the case of a diagnostic test) or investigated (in the case of research). The question is whether and when such unsolicited results should be shared with patients and participants.

There is emerging consensus in literature that results that indicate a susceptibility to conditions that are life-threatening, manageable and unlikely to have been diagnosed without the genetic test ought to be fed back (Eckstein *et al.,* 2014). What this means is that if a diagnostic test reveals the likely development of a life-threatening condition (such as for instance familial adenomatous polyposis), where it is unlikely that this susceptibility would have been diagnosed without the genetic test result, and where a lifestyle or clinical intervention could prevent the development of the said condition, this should be fed back. This could include, for example, regular screening, dietary changes, or surgical

intervention. In addition, ideally there needs to be some indication – preferably because of a decision made during the consent process – that participants would like to receive findings that fulfil these criteria (Appelbaum *et al.,* 2015). An important focus in the latter requirement is that participants should also be allowed a right not to know, (Jarvik *et al.,* 2014; Cowley, 2016) although this requirement has come under challenge (Burke et al., 2013; Berkman and Hull, 2014). Where results fall in this category, they should be fed back both in the research and in the clinical context. Beyond this apparent consensus however, there remain a number of important and unresolved issues that should be considered in the South African context. For example, the question in a research environment remains as to who would be responsible for the costs of validation tests and genetic counselling during the process of feeding back results, as discussed below.

#### 5.2.5.1 Which Findings Should be Fed Back?

As outlined above, there seems to be consensus that findings that point to clear medical or clinical benefit should be fed back, and we would broadly support this approach. However, there is controversy about whether results that do not fall in this category should also be fed back, particularly where there are currently no clinical or lifestyle interventions that could avert or delay the development of this condition. Similarly, there may be genetic findings indicating a predisposition to developing conditions that are not life-threatening but could inform on matters otherwise important to the individual, for instance relating to potential drug toxicity.

There is also a challenge in determining which results to feed back, and this relates to concerns about the evidence to support whether particular variants are disease-causing. The quality of evidence rests in part on whether a sufficient number of studies have been done in the given population to affirm that variants are similarly penetrant (Kircher *et al.,* 2014). Most genomic research studies involve Caucasian populations, with only a very gradual increase in the number of non-Caucasian, African or South African participants participating in such research (Popejoy and Fullerton, 2016). This means that most knowledge about which variants may be pathogenic, is based on information pertinent to Caucasians rather than to other population groups. Obviously, such knowledge may not be relevant to most of South Africa's population. This has clinical implications. For example, a recent study found that variants classified as being involved in causing hypertrophic cardiomyopathy may not be pathogenic in African-American populations (Manrai *et al.,* 2016), meaning that African-American patients may have been given the wrong interpretation of their genetic information. This outcome has strong implications for South Africa's population if indeed the African heritage is the distinguishing factor.

No consensus exists currently about whether participants should be informed of so-called variants of unknown significance that have an unknown effect on disease causation. In this case, it is not known whether identified variants found in

genes known to play a role in disease causation may be pathogenic. Receiving feedback on a variant of unknown significance can cause considerable anxiety and lead to potentially unnecessary clinical interventions (Culver *et al.*, 2013). Another challenge is that these variants of unknown significance may subsequently (in the years following a genomic screen) be reclassified as either pathogenic or benign, which would be highly relevant for participants to know. The question is whose responsibility it should be to keep track of these variants, and to re-contact patients or participants should variants be thus re-classified.

#### 5.2.5.2 Replicating and Validating Findings

In a research context, feedback of genetic results should only be done once a repeat sample has been taken and the results replicated using diagnostic-standard procedures designed to reduce errors, sample mix-ups and so forth. Internationally, best practice is to validate pertinent research results in an accredited diagnostic facility (Presidential Commission for the Study of Bioethical Issues, 2013; Kaye *et al.,* 2014) and preferably to obtain a second sample according to diagnostic criteria. Adding this best practice requirement to the research context could significantly increase the cost of research, and provides a reason for researchers to not return research results, even those that have clinical merit if verified.

#### 5.2.5.3 Who Should Provide the Feedback of Findings?

A final question relates to who should feedback pertinent genetic findings in the clinical and research contexts, particularly when such findings are outside the scope of clinical expertise of the consulting doctor or researcher. Generally, the literature indicates a preference for such findings to be fed back by medical genetic health professionals, preferably genetic counsellors. South Africa has a significant shortage of health professionals with these qualifications. For instance, in 2013, reports showed that only 11 registered medical geneticists, 42 medical genetic scientists and technologists and ten genetic counsellors serviced the country – and not all registered health professionals actually worked in their field of training (Kromberg and Krause, 2013; Kromberg *et al.,* 2013). Excluding research staff, this translates to one clinical genetic professional per 2.5 million people. By comparison, the median across nine European countries, including less wealthy nations, like Bulgaria and the Czech Republic, is one clinical genetic professional for approximately 195 000 people. While the number of trained clinical professionals has since grown, the need for their services has also grown with the number of genomic studies being conducted in the country increasing exponentially.

A challenge relates to whether South African genetic counsellors are currently equipped to interpret and feedback results of whole genome tests. The nature of the genetic counselling profession has changed considerably with the growing relevance and availability of genomic tests and results (Biesecker *et al*., 2013; Ormond, 2013; Austin *et al.,* 2014), although some authors talk about

these changes as 'evolution rather than revolution' (Wicklund and Trepanier, 2014). The increasing use of genomic tests has forced genetic counsellors to expand their skill set and to devote more time to exploring and explaining test results, rather than time for counselling, which has led to changes in the training curriculum for genetic counsellors elsewhere in the world (Ormond, 2013). Currently in South Africa, genetic counsellors are not yet trained in the interpretation of whole exome sequence (WES) or whole genome sequence (WGS) results, but their curriculum should arguably evolve to incorporate such skills.

The question arises as to whether clinicians and other medical practitioners are adequately equipped to feedback results to participants/patients? Although anecdotal, the answer to this is probably that medical curricula in South Africa currently do not cater for the rapidly evolving field of genomics and genetics. Thus, as for genetic counsellors, it is important to adapt curricula at a national level to cater for this deficiency.

#### 5.2.5.4 Return of Results to Children

Deferring genetic testing of adult onset genetic disorders is often justified by the fear of discrimination and stigmatisation, the lack of medical utility and the possibility of misinforming the child in the future about their test results. On the other hand, one possible justification for the testing of children for adult onset disorders is that, although there may be no known interventions at this point in time for a specific condition, some parents may believe that the information is a benefit in itself, which may assist them with pre-emptive strategies, such changing their child's diet, to keep abreast of new interventions, or to be prepared for the onset of symptoms.

### 5.2.6 South African Human Genetics Advisory Board

A specialist national SAHGAB could provide genetic and genomic advice at the national level. Although the terms of reference would need to be carefully considered, this board could review evidence for the scientific and analytical validity and clinical utility of genetic tests that are being offered to patients, both in the public and private health care services. This board should be located where it will create the most benefit in the national health context, not excluding the possibility that it could fall under the auspices of an existing structure, e.g. the DoH. A key aspect is that it should be independent and take an unbiased view in the interest of society at large.

Such a board could provide the necessary guidance that is required at the national level in developments of genetics and genomics. One example would be the development of companion genetic tests in the field of nutrigenetics or for pharmaceuticals in pharmacogenetics, as well as monitoring of genetic tests available on the market. One important function of such a board would be that it would receive and investigate complaints of misuse of genetic tests in any context. Tests would need to be fit-for-purpose and appropriate, and in

the South African context, this would require vigilance over population-specific variants.

## 5.3 Genomic Custodianship *versus* Ownership

Genomic sovereignty describes the view that those who donate genetic samples and associated data can claim the right and have the power to determine its present and future use. It usually refers to groups of people with an identifiable cultural or territorial identity, rather than to individuals. For example, a specific ethno-linguistic group may wish to claim control over the use of DNA samples from their members and wish to exercise genomic sovereignty. As mentioned previously, this model has worked well among the First Nations people of Canada, but the practicalities of implementing a system that gives effect to genomic sovereignty can be challenging. In the context of genomic sovereignty in South Africa, it is unclear what may constitute a unit with an identifiable identity and a single governance structure.

An important and contested question is whether genomic resources can be 'owned' (in the proprietary sense) and, if so, who is entitled to 'own' them (Slabbert and Pepper, 2010). Discussion of this matter is frequently confused and confusing because the nature of the 'rights' being contested are not clarified. If 'legal rights' are to be recognised, a further question is whether 'genomic resources' can be recognised as property within the prevailing proprietary rights framework, given that e.g. revealing a DNA sequence is a discovery and not an invention. These topics have received little analytical attention in South Africa to date. Current discussion assumes without justification that 'ownership' and other proprietary rights are both possible and desirable in respect of genomic resources. This is notwithstanding that, traditionally, South African law does not recognise human body parts, including biological samples, as constituting 'property'. This legal fact supports the view that genomic resources should be a common good, i.e. public property which is outside of commerce and thus not open to private ownership.

An implication of giving effect to the notions of genetic sovereignty claims and genomic resources as a common good is that the State would take responsibility for providing the infrastructure to govern and manage access to and (re)use of samples and data. The governance system could include representative input from donors. South Africa is familiar with the notion of State custodianship (similar meaning to stewardship) of natural resources in the form of water and of mineral resources. Infrastructure and governance systems are designed to manage exploitation, protection, sustainability, and fair access to those resources and a form of redistribution or benefit sharing. There is no obvious reason, thus, why stewardship of genomic resources should not successfully recognise sovereignty over genomic resources in light of stewardship principles.

Clearly, a major contradiction is evident between the view that regards donors as contributors to the common good, on the one hand, and that which regards

those who work with genomic resources as entitled to proprietary or other rights recognised and protected by law, on the other. Other views include that the 'right of control' – whether legal or symbolic – could lie with the individual who provided the genomic resources for research, or with the population groups that they are members of, or with the researchers who build up repositories of samples and data, or with their institutions, or with national entities, such as national governments (Petrini, 2013). Arguments exist for and against the various positions. The San population objected to previous genomic work involving San elders (Schuster *et al.*, 2010), which was perceived as inappropriate and potentially exploitative by official San leadership. Subsequently, the leadership developed a guideline that it regards as more ethical outlining the expectations (both ethical and operational) of those who wish to conduct research with San communities, including genomics research.

International collaborative research requires careful consideration of the importance ascribed to custodianship *versus* ownership, which may differ among collaborating partners. An International Charter of Principles for Sharing Bio-specimens and Data has recently been published based on the observation that "Contradictory legal and ethical frameworks across national borders are obstacles to effective sharing: more specifically, the absence of an integrated model proves to be a major logistical obstruction. The Charter intends to amend the obstacle by providing both the ethical foundations on which data sharing should be based, as well as a general Material and Data Transfer Agreement (MTA/DTA)" (Mascalzoni *et al.*, 2015).

Our view would be to apply the principle of 'custodianship' or 'DNA on loan' and to avoid the notion of ownership. This topic should however be carefully and vigorously debated and clarified for the South African context, preferably by the South African Law Reform Commission, since it affects a cascade of implications like the ethical values of equity and distributive justice, as well as the good governance principles of benefit sharing and also whether intellectual property can exist if genomic resources are to be regarded as a 'common good'.

## 5.4 Benefits and Benefit Sharing

Benefits flowing from genomic work can be material (financial or other tangible benefits) or in other forms, e.g. capacity building, health care, knowledge generation, etc. It is an important distinction as the financial gains that are often foreseen in research and development are either unrealistic or do not materialise in the short term.

The Human Genome Organisation (HUGO) Ethics Committee defines individual and community benefit as social goods: "A benefit is a good that contributes to the well-being of an individual and/or a given community (e.g. by region, tribe, disease-group…). Benefits transcend avoidance of harm (non-maleficence) in so far as they promote the welfare of an individual and/or a community.

Thus, a benefit is not identical with profit in the monetary or economic sense. Determining a benefit depends on needs, values, priorities and cultural expectations." (HUGO Ethics Committee, 2000).

A key challenge regarding benefit sharing discussions in genomics is that people give their samples voluntarily and without expecting any reward, i.e. the gift model, while scientists and other downstream entities may acquire enhanced credentials and benefits, including wealth because of working with the samples and their associated data.

### 5.4.1 Rationale for Benefit Sharing

The conceptual view of genomics work, as well as the prevailing proprietary system, informs attitudes about benefit sharing. If genomics work is regarded as a common good, then it follows logically that a benefit sharing framework will benefit society at large and that no specific agreements need to be in place. If genomics work is regarded as just another branch of scientific work that acquires its materials via the gift model, then the rationale for benefit sharing is less obvious, and should be regulated.

Currently, recruitment information for potential providers of biological samples usually speaks of the noble cause of contributing to future improvements in health care and human well-being. Guidelines for genetic and genomic work generally discourage or even forbid payment for biological samples. Yet, these same guidelines permit or even encourage commercialisation of data obtained from samples. The ethical contradiction is obvious: reward for labour is accepted but payment for one's biological sample is regarded as unethical.

In South Africa, it seems appropriate to adopt an inclusive view: we share in all genomics work but have different roles. Some of us provide materials, others do the actual work, and yet others manage how the samples and data can be exploited to maximum benefit by sharing and increasing knowledge optimally. This inclusive view accords with the philosophy of Ubuntu, which promotes reflection on how, no matter our diversity, we are all connected and dependent on recognition by others. This model is reflected in the nature of genomics work, which requires not only large sample sets but also multiple contributions in order to maximise its value to society.

Health care and research have conventionally viewed themselves through a mono-cultural lens i.e. a developed world view that claims neutrality. This view is generally inaccurate since scientific work is not neutral and, in South Africa, this view is clearly inappropriate. The ethical contradiction inherent in the conventional gift model for obtaining samples for scientific work must be addressed for genomics work. Consequently, it seems obvious that a form of benefit sharing is required. This ties in to the benefit sharing required for bioprospecting, and this should also be addressed.

### 5.4.2 Model for Benefit Sharing

Accepting the need for a form of benefit sharing, the next issue is how benefits may be shared amongst donor communities and society at large (Knoppers *et al.,* 2014; Mahomed and Sanne, 2015). Tangible benefits can range from monetary awards to employment opportunities and business development. Intangible benefits can include capacity and skills building, as well as generation of new knowledge (Lairumbi *et al.,* 2008; Lairumbi *et al.,* 2012). An important contextual benefit is the development of research capacity and infrastructural development, e.g. development of bioinformatics resources and capacity to do analysis of data, or development of biobanking facilities in South Africa to facilitate future research.

An appropriate universal model for benefit sharing is yet to be described. This is largely because people regard it as a legal issue, flowing from whether exclusive rights to biological samples are recognised and protected by the law. Providers of biological samples are expected to do so as a gift on the basis of altruism, while researchers or their employers may use those 'gifts' for commercial or career building purposes.

The essence of the model described by Haddow *et al.* (2007) is that benefit sharing is a core principle because the information contained in DNA is communal, and public administration and promotion of health are a common good. The model gives effect to the principle of distributive justice, the value of Ubuntu, through preventing ownership (in the proprietary sense) by anyone, while permitting control by the 'donor', and allocates responsibility for ensuring fairness and equity to the state. Applications to use genetic or genomic resources must include a benefit sharing proposal that must satisfy a standing committee (either institutional, provincial or national). Ethics approval of research proposals is essential, by either an institutional, provincial or a national REC.

### 5.4.3 Benefits – Researcher, Institution and Commercial

From an ethical perspective, benefits are usually viewed broadly in the context of risks. This originates from a balancing of the principles of beneficence and non-maleficence. In medical interventions and research, assessing the risk-benefit ratio is an important calculation. Furthermore, upholding the principle of justice in research requires that those who bear the burdens of research must also stand to benefit (The Belmont Report, 1978). Benefit in research includes both individual and societal benefit. In the context of genetic and genomic research, benefit to individual patients or research participants is linked to return of results. This will further depend on whether results are clinically actionable or not. It follows that the perception of benefit is greater with clinically actionable results that improve the health of the patient or research participant. In addition, results that protect patients or research participants from future harm would also be regarded as beneficial.

Researchers may benefit at an individual level in the form of academic publications and conference presentations, academic promotions and research grants. Institutions benefit broadly from research outputs, related financial subsidies and academic prestige. Commercial entities stand to benefit financially in various ways depending on the type of research. In this regard, direct to consumer marketing for genetic and genomic testing by private entities is particularly concerning (Dandara *et al.,* 2013).

Societal benefits are more broadly perceived as beneficial in scientific progress. This has application in genome-wide association studies to identify genetic variants that are associated with disease traits. Although such research is important in developing knowledge and providing new insights into biological processes for underlying disease, it is equally important to understand that the associated markers usually have very low predictive value and should therefore be used with great care.

How communities perceive benefit may differ from the perspectives of researchers and other stakeholders. Some communities have an expectation of benefit or profit sharing as a research-related benefit (Moodley *et al.,* 2014). Other communities cite scholarships and employment for members of communities where research is conducted (South African San Institute, 2017). The concept of benefit sharing for genetics and genomics research thus requires further consideration and debate in South Africa.

## 5.5 Intellectual Property Rights and Commercialisation

The nature and scope of IP rights and the potential for commercialisation depend on the outcome of the investigation into whether genomic resources are to be regarded as a common good and thus are outside the domain of private property.

If it is assumed that genomic data represent discovery and not invention, the aspect of how IP will accrue from genetic and genomic data is simple. Data need to be 'productised' into a service or a product before they can attract IP rights. An example of such a service would be the mining of the data to reveal a specific attribute in the data that was not obvious before. A product would be to use the data to design, e.g. a drug that targets a specific sequence signature or a diagnostic test that is designed to detect a specific signature in the sequence. However, a product could also be the compilation of the genetic data in a unique manner.

The benefits of commercialising the above service or product will accrue in the bio economy and these benefits are easily distributed if a pre-arranged model exists for its distribution. When genomic and genetic data are used for the purpose of generating benefit, the benefit should be distributed in an appropriate manner, and not just accrue to the public-private entity that innovated with the data. Benefit should reach the group or community whose genetic material was used to generate the data.

## 5.6 Regulation

The current state of affairs in South Africa indicates that unethical practices are left unchecked, for various reasons. The need for effective regulation with strict sanctions is acute.

Regulation should be at various levels, starting with the individual practitioners that need to be regulated by professional bodies, their own institutions, and bodies mandated to do so. Although ethics policies are in place at, for example, institutions, they are not enforced or the sanctions for violation are minimal. To eradicate unethical practice, which has the potential to harm the health care of society, there should be no tolerance for unethical practice at any level.

It is also evident from the issues discussed in the section on accountability (section 5.1.1) that there are several aspects that require regulation in terms of genetics and genomics in South Africa. Most obvious is the operation and regulation of genetic diagnostic testing services. The sanctions for not adhering to best practice and international and national standards should be severe, since left unchecked this is a high risk to the genetic health care of society.

Biobanks and bio-repositories (section 5.2.3) need regulation to allow un-compromised storage of genetic material. Lack of regulation in this regard will allow the *status quo* to continue, where various levels of quality are adhered to, not all in the national interest. Flowing from the regulation of samples in biobanks, the data emanating from those samples should also be regulated. Caution is advised regarding the potential for involvement of funders in the development of the policy documents and the dependent relationships that may develop between funders and grant recipients.

Aspects such as benefit sharing (section 5.4) require regulation, to allow for an open relationship between scientists and the population that builds trust over time. It is only when society and experts view the regulation as effective, that maximum benefits could be generated by all of us working together to enhance health at the national level.

Some of the aspects mentioned above have been regulated in the past in South Africa. However, the regulation has not had the desired effect, the reasons being multifactorial. What is required at present is strong, clear and effective regulation with appropriate sanctions. The sanctions should have the aim to remove certain practices and practitioners from the field of genetics and genomics, as not doing so continues to work against the positive impact that genetics and genomics holds for our population.

International collaborative research may present with complexities and differences in interpretation that need to be considered. Specific issues, in addition to those mentioned in this section include ownership *versus* custodianship (section 5.3), intellectual property (section 5.5) and DNA storage, import and export (section 5.2.2).

## 5.7 Recommendations – Good Stewardship

### R9. Code of conduct

A code of conduct and best practice for professionals working in the field of genetics and genomics in South Africa should be developed by government and other appropriate entities to promote good stewardship of resources including data and biological specimens.

### R10. Policy and guidelines appropriate for the South African context

The following should be developed by government and other appropriate entities:

a) Guidelines for the oversight of responsible clinical genetic/genomic testing, including appropriate accreditation of laboratories offering genetic/genomic testing and monitoring of staff qualifications and expertise.

b) An appropriate national policy that outlines obligations, mechanisms and circumstances for feedback of individual results.

c) Policies and guidelines to promote good stewardship of resources in clinical and research settings to promote innovation and translation of research into clinical practice.

d) A national governance framework for South African biobanks that includes integrated data storage systems that have the potential to enhance health care and justice (i.e. in forensic and legal contexts), and to maximise their value to society.

e) A national framework for sample and data access to promote equitable and responsible sharing of genetic and genomic resources to enhance knowledge generation and translational science, drawing on existing international and continental policies.

### R11. South African Human Genetics Advisory Board

A South African Human Genetics Advisory Board (SAHGB) should be established. The board should have appropriate expertise to provide guidance to policy-makers and regulatory structures.

### R12. Open debate with stakeholders and policymakers

Debate, explore and adapt the 'sociologically informed model' for the principles of (a) custodianship/ownership of samples and (b) benefit sharing in South Africa. Include relevant stakeholders like the National Intellectual Property

Management Office (NIPMO) and the South African Law Reform Commission, since the topics affect a cascade of implications: ethical values of equity and distributive justice; good governance principles of benefit sharing; whether intellectual property can exist if genomic resources are to be regarded as a 'common good'.

### R13. Legal framework

a) Laws and regulations relating to genetics and genomics must be aligned and contradictions must be carefully and comprehensively addressed.

b) The South African Health Products Regulatory Authority (SAHPRA) should regulate genetic tests under the Medical Devices Act *(No. 14 of 2015)*.

c) The Criminal Law (Forensic Procedures) Amendment Act *(No. 37 of 2013)* and its Forensic DNA Regulations (2015) must be updated.

d) The potential value of a mutually beneficial Memorandum of Understanding between the South African Council for Natural Scientific Professions (SACNASP) and the Health Professions Council of South Africa (HPCSA) must be explored for forensic practitioners using DNA testing (See also **R15** and **R18**).

# 6 Overarching Recommendations

South Africa needs to develop a set of guidelines and policies to address the ethical, legal and social implications of genetic and genomic work. The recommendations need to be ethically and legally sound, culturally appropriate, feasible, enforceable and sustainable given the resources within the country and balanced against competing national priorities. Our South African genetic heritage is locked within our genomes. It is a treasure trove that will provide fascinating insights onto our past and will inform our health and susceptibility to diseases.

Recommendations in three main areas, Building Relationships, Respect for Persons and Good Stewardship, have been provided and these culminate in a set of overarching recommendations.

### R14. Capacity development in genetics and genomics in South Africa

South Africa is currently in short supply of appropriately trained and skilled personnel at all levels of genetics and genomics work. To establish, build and maintain a service platform and large scale, sustainable genomics programmes for the benefit of a healthy nation, bearing in mind ethical, legal and social responsibility, will require technical, scientific, computational, bioinformatics and statistical analysis, as well as financial, legal and ethical expertise. More resources are therefore required to support genetic and genomic work, including training of genetics nurses, genetics counsellors, medical geneticists, medical scientists, bioinformaticists, biostatisticians and forensic scientists for the public and private sectors in South Africa.

### R15. Legal framework with policies and guidelines for genetics and genomics in South Africa

Legislation and policies should be developed in an inclusive and cross-cutting framework, taking into account national, regional and international contexts, and should avoid stifling innovation.

### R16. South African Human Genetics Advisory Board

The SAHGB should be adequately resourced and independent, with the aim of providing oversight in genetics and genomics at the national level and working in concert with ethics and legal regulatory structures.

### R17. Ethical oversight

Ethical implications that are deemed problematic by research ethics committees, researchers, patients/participants or the public should be brought to the attention of the NHREC whose direct involvement in policy-drafting should be sought.

### R18. Legal oversight

Legal implications should be brought to the attention of the South African Law Reform Commission whose direct involvement in policy-drafting should be sought.

### R19. Framework for non-compliance

Sanctions for non-compliance with current and future legislation must be defined, be implementable and be effective.

# 7 Conclusions

The face of health care delivery, biomedical research and forensics in South Africa is rapidly changing as a result of advances in the fields of genetics and genomics. Commensurate with this rapid evolution is the need to consider the ethical, legal and social implications of these technological advances. Implicit in this consideration is an understanding of African philosophy, and in particular the notion of Ubuntu.

This report has addressed what we consider to be key imperatives in genetics and genomics ELSI, and we have developed a set of recommendations which we believe could inform the drafting of one or more policy documents that will guide the drafting of legislation, regulations and guidelines/standards to regulate genetics/genomics and associated areas (e.g. biobanking) in South Africa. The framework must demonstrate that governance processes and procedures are infused with integrity, honesty, responsibility, accountability and efficiency. It must be informed by legislation and regulations that govern human biological materials and are compliant with international standards. The framework should be reasonable, feasible, pragmatic and non-stifling for the South African context.

The important conceptual issue of whether biological samples, including DNA, may be recognised as 'property' under South African law must be rigorously debated and clarified, preferably by the South African Law Reform Commission. This issue is different from the current pattern of permitting IP rights in terms of current law. The convention that 'donors' provide their samples voluntarily without reward (the gift model) is rejected increasingly by those who do not accept that researchers and other downstream entities may acquire enhanced credentials and wealth as a result of working with the samples and their associated data. The implication is that benefit sharing is a logical part of the genomic project. The 'sociologically informed model' for benefit sharing includes the idea that some commercialisation of genetic and genomic research is acceptable.

Finally, the involvement of the 'public' and 'communities' should be integral to the policy-drafting process. Deficiencies in our understanding of precisely what constitutes communities and how they should be implicated are recognised. This matter should be addressed as a matter of urgency to ensure that participation is optimal.

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Health Professionals Act *(No 56 of 1974)*.
Medicines and Related Substances Act *(No 101 of 1965)*.
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National Health Act *(No 61 of 2003)*.
Natural Scientific Professions Act *(No 27 of 2003)*.
Promotion of Access to Information Act *(No 2 of 2000)*.
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## 8.3 South African Regulations

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# Appendix A: Composition of Study Panel

## A.1 Chairperson of the Study Panel

### Michael Pepper

Prof Michael Pepper (MBChB (Cape Town), PhD (Geneva), MD (Geneva), Privat Docent (Geneva)) is Director of the Institute for Cellular and Molecular Medicine, Director of the South African Medical Research Council (MRC) Extramural Unit for Stem Cell Research and Therapy and a research Professor in the Department of Immunology in the Faculty of Health Sciences at UP. He is also Professeur Associé in the Department of Genetic Medicine and Development in the Faculty of Medicine at the University of Geneva, Switzerland. He obtained his MBChB in 1982 from the Faculty of Medicine at UCT, and moved to Geneva in 1986, where he obtained his PhD in 1990 and MD in 1992. In 1997, he obtained his Habilitation and had the title Privat Docent conferred on him. He returned to South Africa in July 2004. Prof Pepper has worked extensively in the field of clinically-oriented (translational) molecular cell biology, and his interests include stem cells and the human genome. He is co-responsible for the Southern African Human Genome Programme which was launched in January 2011. Prof Pepper is part of a team which assists the National Department of Health with legislation concerning human tissues. He is President and Chairman of the Board of the South African Tissue Bank Association. He was until recently a member of the National Advisory Council on Innovation which advises the Minister of Science and Technology. Prof Pepper has >260 medical and scientific publications with an H-index of 70/81 (Scopus/Google Scholar), and has received a number of awards for his research. He has been extensively involved in teaching at undergraduate and postgraduate levels and is frequently solicited as a speaker at local and international meetings. He is on several editorial boards and interacts regularly with the media and writes for the lay press on medical and scientific matters.

## A.2 Members of the Study Panel

### Collet Dandara

Prof Collet Dandara is a full Professor of Human Genetics, specialising in pharmacogenomics. He is one of the leading pharmacogenetics experts in Africa. With support from various funding organisations (MRC, NRF, Southern Africa Consortium for Research Excellence (SACORE)), and colleagues in academia, he has led pharmacogenomics research at UCT. He is a TWAS Young Affiliate/Alumni (TYAN) and represents the sub-Sahara Africa region on the TYAN Exco.

Prof Dandara is a member of the African Society for Human Genetics (AFSHG) and the Southern Africa Society for Human Genetics. He is an advocate of transformation of the research landscape which has seen him train many postgraduate students from previously disadvantaged backgrounds.

## Jantina de Vries

Prof Jantina de Vries is an Associate Professor in Bioethics at the Department of Medicine of UCT. She has broad experience in investigating ethical challenges in African genomics research and has published on a range of topics including the effect of genetic attribution on disease stigma, perspectives on broad consent, community engagement and fair and equitable policy development. She led the H3Africa Working Group on Ethics from 2012 until 2016, is the Co-PI on an H3Africa ELSI Coordinating Centre award from the National Institutes of Health (NIH) and is a member of the Global Alliance Regulatory and Ethics Working Group. Prof De Vries obtained her DPhil at the University of Oxford. Her PhD explored questions around ethnic stigmatisation as a risk in population genomic research in Africa. Her papers have appeared in *Nature Reviews Genetics, Science, PloS Medicine,* the *European Journal of Human Genetics, BMC Medical Ethics,* the *Journal of Medical Ethics* and other leading journals.

## Ames Dhai

Prof Ames Dhai is the Director of the Steve Biko Centre for Bioethics which she established in 2007. It has local and international recognition as a leading centre. She serves on several policymaking bodies in the country, including being a Past-President of the South African Medical Association (SAMA), and the board of the recently established South African Health Products Regulatory Authority. She also serves as an expert advisor for the World Medical Association, the World Health Organisation (WHO), and is on the WHO's African Advisory Committee for Health Research. She participated in activities of the Institutes of Medicine (USA), and the National Academies of Sciences (USA). She is Editor-in-chief of the *South African Journal of Bioethics and Law* and Associate Editor of the *South African Medical Journal.* She can be credited with entrenching bioethics as an integral aspect of health sciences in South Africa. She is the recipient of several awards including SAMA Gender Acclaim Award (2012), the SAMA Certificate Award (2012) in honour of patriotism, courage and contribution made in the struggle for liberation of the medical profession and a joint recipient of the Vice-Chancellor's Academic Citizenship Award (2017). Using an academic platform, Professor Dhai has taken a lead in advocacy including testimony at the Life Esidimeni Tragedy.

## Melodie Labuschaigne (formerly Slabbert)

Prof Melodie Labuschaigne, former Deputy Executive Dean of the College of Law and Director of the School of Law at Unisa, is presently a full Professor in the Department of Jurisprudence in the School of Law, Unisa. She is the recipient of the Unisa's Chancellor's Award for Excellence in Research and the Women in Leadership Research Award, and holds both a DLitt and LLD degree. Her research interests straddle medical law and ethics, legal aspects relating to the application of biotechnology, and the intersection between law and literature.

## Freddy Mnyongani

Dr Freddy Mnyongani is Senior Lecturer in Law at UKZN, Durban Campus. He has lectured at Unisa where he also served as the Chairperson of the Research Ethics Committee of the university and later of the College of Law. He is an attorney who holds the following degrees: BTh (St. Joseph's Theological Institute), LLB (Wits), LLM (Wits) and an LLD (Unisa). His research interests include legal philosophy, ethics in all its facets, public international law and international human rights law.

## Keymanthri Moodley

Prof Keymanthri Moodley is a Professor in the Department of Medicine and Director of the Centre for Medical Ethics and Law, Department of Medicine, Faculty of Health Sciences, SU. In 2017, she was appointed Adjunct Professor, Department of Social Medicine, University of North Carolina-Chapel Hill, USA. Prof Moodley is a family physician and a bioethicist. In 2013, she was rated by the NRF as an established researcher based on her numerous national and international publications, conference presentations, her role on national bodies like the MRC Board and NHREC and her involvement in international organisations – WHO, International AIDS Society (IAS) and National Institutes of Health (NIH) Data and Safety Monitoring Boards (DSMBs). She has worked as principal investigator on clinical trials since 1999, and served on the University Research Ethics Committee. The centre has been designated as a Collaborating Centre in Bioethics by the WHO, one of ten in the world and the first on the African continent. The main activities of the centre include bioethics teaching, empirical research in bioethics and clinical ethics consultation. Since 2011, Prof Moodley has co-hosted an NIH Fogarty programme to develop capacity in Health Research Ethics in Africa in collaboration with the Bioethics Centre, University of North Carolina-Chapel Hill, USA and has graduated 40 postgraduate scholars from ten African countries over the past four years. In 2013, she was awarded a second NIH grant to examine the ethical and social issues associated with HIV cure research. In 2015, the centre was awarded its third NIH grant to explore ethical, legal and social issues related to genomic biobanking. She is a Member of the ASSAf and completed an Executive MBA in 2015. Prof Moodley served as Chair of the MRC REC from November 2016

to February 2018. In 2017, she was awarded her 4th NIH grant to develop a doctoral programme in Clinical and Research Ethics. Prof Moodley has recently been appointed to the Scientific Advisory Committee of the European and Developing Countries Clinical Trials Partnership (EDCTP).

## Antonel Olckers

Dr Antonel Olckers co-founded DNAbiotec® in 2001 and has served as its CEO since then. Her expertise in science, innovation and business is integrated in DNAbiotec®. She obtained her PhD in molecular human genetics at UP with research performed at the Johns Hopkins Medical Institutions in Baltimore, MD, USA. After graduation she became the head of the Molecular Biology Group in the Department of Human Genetics (UP), and subsequently was Professor and head of department of the Centre for Genome Research (CGR) at NWU. During her tenure she served on two human research ethics committees, and thereafter on the biosafety committee of Wits. Her research focus was population genetics of African populations, and genetic risk factors for Type 2 Diabetes in different populations.

During her academic career she graduated more than 30 MSc and PhD students. She received the BioFundi Award for Capacity Building for her training and education of scientists in the academic and private sectors. To date, DNAbiotec® has trained scientists and legal professionals from 39 countries, 23 from Africa. Dr Olckers received the Legal Aid South Africa *Pro Bono* Award for the *pro bono* service her company has provided, and continues to provide, to Legal Aid SA with regard to DNA evidence. She has testified as a forensic DNA expert in the high courts and regional courts of South Africa for over 18 years. DNAbiotec® was contracted to develop the first formal forensic science qualification in South Africa, and registered it on the National Qualification Framework (NQF) of the South Africa Qualifications Authority (SAQA).

She serves on the advisory boards of several national strategic bodies, e.g. NIPMO, and has served on the National Biotechnology Advisory Committee (NBAC), which was a sub-committee for the National Advisory Council on Innovation (NACI), as well as two other project teams of NACI in the past. She was previously an extra-ordinary Professor in two departments at UP: Immunology and Forensic Medicine.

For more than a decade she has worked with others to form the first independent forensic science professional body in South Africa. These efforts culminated in the formation of the South African Academy of Forensics Sciences (SAAFS) and she was elected as its first Chairperson in early 2018. Dr Olckers received the BioFundi Lifetime Achievement award in 2018 for her work in biotechnology and innovation across different sectors.

## Anne Pope

Prof Anne Pope (LDipLib, SU; BA LLB, RU; PG Dip (International Research Ethics), UCT) is Emeritus Associate Professor in the Department of Private Law, Law Faculty, UCT. She remains a member of the UCT Faculty of Health Sciences Human Research Ethics Committee; is the Deputy Chair of the Human Sciences Research Council Research Ethics Committee; and is the current Chair of the National Health Research Ethics Council.

## Michèle Ramsay

Prof Michèle Ramsay is the Director of the Sydney Brenner Institute for Molecular Bioscience (SBIMB) and Professor in the Division of Human Genetics in the Faculty of Health Sciences at Wits. Her research interests include studying African population genetic diversity and environmental factors to better understand their role in health and disease. She also does research into the genetic basis of rare monogenic eye and skin disorders (including albinism and keratolytic winter erythema), African population genetics, pharmacogenomics and complex disease traits in African populations. She is co-responsible for the Southern African Human Genome Programme (SAHGP) with a view to exploring precision medicine in an African context. As an active member of the Human Heredity and Health in Africa (H3Africa) Consortium, she promotes ethical genomic research and capacity development in Africa. She is Principal Investigator of an NIH-funded Collaborative Centre under the H3Africa Consortium for Genomic and Environmental Risk Factors for Cardiometabolic Diseases in Africans. She teaches, supervises postgraduate students, hosts postdoctoral fellows and mentors young African scientists. She holds a South African Research Chair on Genomics and Bioinformatics of African Populations and is President of the African Society of Human Genetics.

## Raj Ramesar

Prof Raj Ramesar is Professor and head of the Division of Human Genetics at UCT. He also serves as Director of the MRC Human Genetics Research Unit, and Cancer Association of South Africa's (CANSA) Colorectal Cancer Research Consortium. Prof Ramesar is principal investigator on the Retinal Degenerative Disorders research project. Apart from being involved directly with several established research projects aimed at elucidating the genetic basis of diseases in South Africa, he is currently channelling his energy in setting up research into understanding the genetic basis of the more complex, yet common chronic disorders (e.g. hypertension) in our populations.

## Himla Soodyall

Prof Himla Soodyall is a Medical Scientist at the National Health Laboratory Service (NHLS) and Professor at Wits. Her research has used a molecular genetic approach to elucidate the evolutionary history and genetic affinities of sub-Saharan African populations. She was nominated as a Member of ASSAf in 2003, and currently serves as General Secretary on the ASSAf Council. She is the Chairperson of the Research Development Committee at the NHLS, and actively contributes to the public engagement of science. She received the Order of Mapungubwe, Bronze medal, from President Mbeki in 2005 for her contribution to science.

## Wayne Towers

Prof Wayne Towers is employed as the Academic Advisor in the Faculty of Health Sciences Ethics Office for Research, Training and Support at NWU, South Africa. He trained in the field of molecular human genetics and received his PhD in 2005 after which he completed a postdoctoral fellowship at the Centre for Genome Research, NWU in 2008. Although his basic training was in human molecular genetics, Prof Towers made a career change into the field of research ethics in 2015, after completing a postgraduate diploma in health research ethics at SU. His research focus is currently on genetic epidemiology of non-communicable disease, but he is building a future research track in the ELSIs of genetic and genomic research. Prof Towers is the chairperson of the Health Research Ethics Committee of the Faculty of Health Sciences at NWU and is also an advisory member on other ethics committees within the university.

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*Applying scientific thinking in the service of society*

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# Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implicatior

Academy of Science of South Africa (ASSAf)

Academy of Science of South Africa (ASSAf) & Department of Science and Technology (DST)