CHAPTER ONE

INTRODUCTION

1.1. BACKGROUND

A genomic test is the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. It has diverse purposes, including the diagnosis of disease in newborn, children, and adults; the identification of future health risks; the prediction of drug responses; and the assessment of risks to future children (Hoff *et al*, 2000:377-414).

Complex or multifactorial diseases are defined as diseases that are ultimately determined by a number of genomic and environmental factors (Figure 1). Although there are many technologies and strategies that can be used to detect genomic factors influencing complex diseases, these technologies and strategies have inherent limitations. Infact, the very name "complex disease" suggests that the results from relevant studies will not be simple to decipher. Ultimately, both the detection and precise characterization of a factor's contribution to a complex disease are difficult undertakings, because the effect of any one factor may be obscured or confounded by other factors (Schork, 1997:103-109).

Over the past 30 years, about 1,200 disease-causing genes have been identified by studying well characterized phenotypes and by using gene mapping techniques (Lander& Schork, 1994:2037–2048; Botstein & Risch, 2003:228–237).

The same approach has not been as successful in identifying genetic modifiers of common diseases that have a genetic component as shown by familial aggregation but which do not

follow Mendelian laws of inheritance. Examples include many of the common age-related diseases such as hypertension (Wang *et al*, 2009:226-231), diabetes (Hakonarson, 2007:591-594; Sladek *et al*, 2007:881-885), cardiovascular disease (Wellcome Trust Case Control Consortium, 2007:661–678) and dementia(Waring & Rosenberg, 2008:329–334), which are presumed to be determined by several genes (epistasis), and their interaction with environmental factors (gene-environment interaction). These diseases constitute a large public health burden and the discovery of genetic profiles that can be used for disease risk prediction, prevention or treatment is one of the priorities of modern "personalized" medicine.

1.2. OBJECTIVES

To examine the knowledge, attitudes and practice of Nigerians towards genomic tests and to identify how the knowledge, attitudes and practice correlate with gender, age, religion, education and related factors.

1.3 STATEMENT OF THE PROBLEM

Genomic tests for complex diseases are increasingly available for complex diseases such as diabetes, cancer etc. Given their increasing use and substantial reduction in cost, it is inevitable that tests will soon be available in Africa.

This may raise some particular concerns because:

a. Majority of Africans are poor and have high levels of illiteracy, the level of comprehension of genomic and genomic risk of diseases is therefore uncertain. While the concept of heritability is well known, subtle differences such as those between Mendelian or Multi-gene risk of disease may be more difficult.

b. Africans have specific beliefs about origin of illnesses and health, and this may affect their willingness to do these tests, believe the results and act on the results.

c. Africans have specific stories of origin, kinship and personhood that may be challenged by the result of genomic tests and the impact of such interventions on sense of identity is unknown at this time.

d. Africans may not have ready access to interventions that will change the outcomes if they know their genetic risk of certain diseases. This raises questions about the ethical implications of conducting such tests and whether the researchers/test laboratories have an obligation to provide the required interventions.

1.4. RESEARCH QUESTIONS

1. What is the current understanding of Nigerians about genomic tests and their utility in disease prevention, diagnosis and treatment?
2. What is the role of culture, religion and socio-economic status in the perception of the utility of genomic tests for disease prevention, diagnosis and treatment?
3. How do Nigerians view testing unborn babies and children?
4. Will Nigerians want their genomic test results disclosed to a third party?
5. What is their attitude and perception of the risks of Direct-To-Consumer (DTC) genomic tests?

1.5. JUSTIFICATION FOR THE STUDY

The identification of disease-related genes has led to an increase in the number of available genomic tests that detect disease or an individual's risk of disease. As the number of these tests increases, their use and interpretation and the information they generate will require basic understanding of how genomic principles apply to different health problems.

Information about this new advancement in science grows daily all over the world but, there are currently no published studies on knowledge, attitude and use of genomic tests among health care providers and general public in Nigeria. Such data are needed to make educational and policy interventions hence this study is being conducted.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 What are Complex Diseases?

Complex diseases are those caused by a combination of genomic, environmental, and lifestyle factors, most of which have not yet been identified. Vast majority of diseases fall into this category, including metabolic diseases like hypertension, diabetes mellitus, metabolic syndrome, cancers, mental health diseases, autoimmune diseases and many more (Hunter, 200:287–298).

2.2 Risk factors for Complex Diseases

Because of the multifactorial etiology of complex diseases, we tend to discuss these in terms of risk factors. They fall into 2 broad categories, genomic risk factors and non-genomic or environmental risk factors. Genomic risk factors are heritable factors encoded in our DNA that determine protein expression and influence the development of health and diseases. Although we inherit genes associated with these diseases, genomic factors represent only part of the risk associated with their phenotypes. A genomic predisposition means that an individual has a genomic susceptibility to developing a certain disease, but this does not mean that a person harbouring a genomic tendency is destined to develop the disease. The actual development of the disease phenotype depends in large part on a person's environment and lifestyle. Indeed, the interplay between genomic and environmental factors in complex disease continues to challenge researchers (Risch, 2003:228–237). Examples of genetic risk factors include BRCA 1 gene and breast cancer risk. Non-genetic risk factors that are also generally known as environmental risk factors are non-heritable, non-genetic factors that

interact with our genes to cause disease or health. These include factors such as dietary intakes, physical activity, smoking and environmental pollution.

2.3 Genetic Risk Factors for Complex Disease

Genetic factors affect complex diseases risk in several ways. The commonest pathway is through variation in the pattern of genetic inheritance such that specific changes occur in the sequence of DNA leading to changes in gene function, expression or interactions. Whereas 99% of human DNA sequences are similar across all individuals, the human genome is littered with random variations in the arrangement of the nucleotides that constitute the DNA. One example of the variations that can occur is **Single Nucleotide Polymorphisms (SNPs)** -where a base pair in the DNA sequence is replaced by another one (Figure 1) SNP is defined as single base pair variations that occur in at least 1% of the population. These SNPs occur once in every 100 to 300 of the 3 billion base pairs and 30,000 genes of the human genome. These base pair changes lead to different outcomes (Figure 2) depending on the gene affected, type of change that is caused and ability of the cell to repair or utilize alternative pathways. The resultant change in the DNA

Figure 1: Showing substitution of base pairs

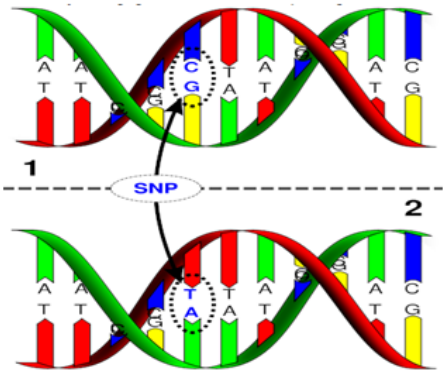


Figure 2: Effect of SNPs

- Consider this sentence

  the fat cat saw the red dog
- Think of each word as a 3 letter code of for the 3 base pairs of DNA that encode an amino acid
- A SNP is a change in the letters. For example
- *insertion* – introduction of a new letter which is not part of the sequence will make the sentence meaningless

  the rfa tca tsa wth ere ddo
- *deletion* – removal of a letter will do the same

  the fatc ats awt her edd

sequence leads to different types of mutations in the genes as shown in Figures 3 and 4.

SNPs have been the most commonly studied type of genetic variation and risk of complex diseases. Many studies have combined SNP analysis with environmental risk factors in order to clarify the attributable risk of each factor in multivariable models. Another type of variation in the human genome is **copy number variations** (CNVs). In this situation, sections of the DNA repeat itself unnecessarily many times. About 12% of the human genome is copy number variable and about 10% of all genes is encompassed by CNVs. More recently attention is also being focused on Epigenetics. Epigenetic changes are believed to lie behind some observed phenomena where, in the presence of similar genotype, cells maintain different terminal phenotypes.Unlike genes that are largely fixed throughout life, epigenetic changes vary from tissue to tissue, change with age, and are susceptible to environmental influences. Studies of monozygotic twins, for example, have shown that whereas they have similar amounts of DNA methylation while young, these amounts differ considerably as they age.

Figure 3: Examples of effects of SNPs

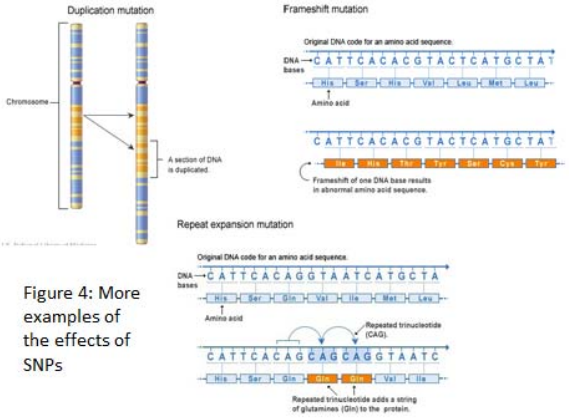


Figure 4: More examples of the effects of SNPs

It is important to differentiate the 2 different types of genomic risk of complex diseases. In some cases, the genetic risk has high penetrance but low prevalence – these have been dubbed Mendelian – and examples include the breast cancer genes – BRCA1 and BRCA2. Individuals with these types of genetic risk factors have a very high chance of developing the associated disease. The second category is the multi-gene disorders where the genetic risk factors have low penetrance but high prevalence. The individual genes here tend to contribute only small amounts to the overall risk of disease and testing for these genes are typically predictive of an altered but often not significant risk.

With current state of knowledge, rather than studying genomic and environmental factors separately, researchers are now combining studies of genetic and environmental factors and how they interact with one another. By looking at the whole picture, researchers can identify genomic risk factors, which may in turn be modified in an environment-specific manner (Dempfle *et al* 2008:1164-1172).

2.4 Methods of studying genetic risk of complex diseases

2.4.1 The Human Genome Project and New Approaches in Gene Searching

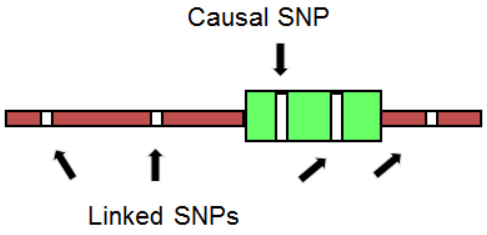
The completion of the Human Genome Project has changed how researchers approach complex diseases by revealing new insights to the genetic risk of complex diseases. By sequencing the entire human genome and making the sequence available on free to all scientists, this has enabled studies of the association of SNPs to assess disease risk.

2.4.2 International Haplotype Mapping Project (HapMap)

This project was conceived to take advantage of linkage between SNPs that are associated with diseases – causal SNPs – and adjoining SNPs that occur with them. Using these

linkages, the human genome was broken into haplotype blocks and these blocks were studied for disease associations (Figure 5) (Weiss & Terwilliger 2000:151-157). Specifically, "tag" SNPs within haplotypes are identified and then used to uniquely identify those haplotypes.

Figure 5: Defining Haplotype blocks for Association Studies



The HapMap has enabled another tool for discovery of disease-allele association and that is the Genome-wide Association Studies (GWAS) methodology which has emerged as a powerful approach for identifying genetic variants influencing common, complex diseases and traits(Hunter *et al,* 2007:870–874; Sladek *et al*, 2007:881-885; Wellcome Trust Case Control Consortium, 2007:661–678; Yeager *et al*, 2007:645–649; McCarthy & Hirschhorn 2008:156–165). Nearly all GWAS to date have concentrated on detecting and characterizing main effects and have not fully explored the potential role environmental factors play in modifying genetic risk.

2.5 Strategy in Complex Disease Mapping

Functional Candidate Gene Approach is a productive and cost effective strategy used in complex disease mapping. It involves identifying and typing SNPs in candidate genes. Expression studies using microarray technology and genomic mapping data from both human and animal models of common disease will continue to highlight many suitable candidates for this kind of analysis.

The candidate gene strategy can be approached in two ways: either by assembling a relatively large collection of potential disease genes and concentrating on scanning coding sequences for potential functional coding SNPs (cSNPs); or by focusing on a single gene and systematically scanning all of its genomic sequence for all polymorphisms. There are obvious

advantages and disadvantages to both these methods. Restricting the search to cDNA sequences alone could result in failure to detect a predisposing variant located in a noncoding regulatory region of the gene. In this situation, it is hoped that at least one cSNP would be detected that was close enough to be in linkage disequilibrium (LD) with the functional variant and, therefore, still capture the disease association. However, LD is not only dependent on physical distance, however, but also on differing allele frequencies and the age of the mutation. This is illustrated in the analysis of allelic associations between SNPs in the lipoprotein lipase (LPL) gene, in which it was not possible to assume any SNP would 'give reliable information about flanking sites' and that a random sampling of three or four SNPs in the 10 kb analysed 'would not be a reliable method of detection of nearby causal variation'. If typical, these effects will result in considerable loss of power to detect any predisposing disease alleles using this method.

The advantage of scanning the entire genomic sequence of a gene is that, providing enough individuals are analysed, the investigator stands every chance of capturing and testing all potential functional polymorphisms; however, until an inexpensive 'off the shelf' SNP scoring technique is widely available (in the penny/genotype range), for the majority of laboratories this approach will only be feasible if there is already prior evidence that the region is linked and/or associated to disease(Clayton & McKeigue 2001:1356–1360).

2.6 Genomic testing

Genomic testing is "the analysis of, chromosomes (DNA), proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes"(Manolio *et al*, 2007:1045–1051). It can provide information about a person's genes and chromosomes and their association with risk of health and disease throughout life.

In gene tests, scientists scan a patient's DNA sample for mutated sequences. A DNA sample can be obtained from any tissue, including whole blood or a mouthwash sample. DNA can also be extracted from fresh or stored tissue collected during surgery, from cultured cells, hair roots, archived biopsy specimens and numerous other sources.

For some types of gene tests, researchers design short pieces of DNA called probes, whose sequences are complementary to the mutated sequences. These probes will seek their complement among the three billion base pairs of an individual's genome. If the mutated sequence is present in the patient's genome, the probe will bind to it and flag the mutation. Another type of DNA testing involves comparing the sequence of DNA bases in a patient's gene to a normal version of the gene.

As with other diagnostic testing, clinical assessment of the affected individual, and documentation of the pedigree (family history), are the starting point for genomic testing. This defines which gene/s the laboratory should study. Identifying the mutation causing the disorder is straightforward if a single gene with one or a small number of mutations is identified as causing the disorder. For the vast majority of genomic disorders however there is often the possibility of many different mutations occurring in a host of genes in different families (Gillian *et al,* 2001:233–237).

2.7 Types of Genetic Testing

Available types of testing include:

Newborn Screening: Newborn screening is used just after birth to identify genomic disorders that can be treated early in life. The routine testing of infants for certain disorders is the most widespread use of genomic testing—millions of babies are tested each year in the

United States. All states currently test infants for phenylketonuria (a genomic disorder that causes mental illness if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland).

Diagnostic Testing: Diagnostic testing is used to diagnose or rule out a specific genomic or chromosomal condition. In many cases, genomic testing is used to confirm a diagnosis when a particular condition is suspected based on physical mutations and symptoms. Diagnostic testing can be performed at any time during a person's life, but is not available for all genes or all genomic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disease.

Prenatal Testing: Prenatal testing is used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered to couples with an increased risk of having a baby with a genomic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them decide whether to abort the pregnancy. It cannot identify all possible inherited disorders and birth defects, however.

Pre-implantation Genomic Diagnosis: Genomic testing procedures that are performed on human embryos prior to the implantation as part of an in vitro fertilization procedure.

Forensic Testing: Forensic testing uses DNA sequences to identify an individual for legal purposes. Unlike the tests described above, forensic testing is not used to detect gene mutations associated with disease. This type of testing can identify crime or catastrophe victims, rule out or implicate a crime suspect, or establish biological relationships between people (for example, paternity).

Parental Testing: This type of genomic test uses special DNA markers to identify the same or similar inheritance patterns between related individuals. Based on the fact that we all inherit half of our DNA from the father, and half from the mother, DNA scientists test individuals to find the match of DNA sequences at some highly differential markers to draw the conclusion of relatedness.

Research Testing: Research testing includes finding unknown genes, learning how genes work and advancing our understanding of genomic conditions. The results of tests done as part of a research study are usually not available to patients or their healthcare providers.

Pharmacogenomics: Type of genomic testing that determines the influence of genomic variation on drug response (Hunter *et al,* 2008:105-107).

Carrier Testing: Carrier testing is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genomic disorder. This type of testing is offered to individuals who have a family history of a genomic disorder and to people in ethnic groups with an increased risk of specific genomic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genomic condition.

Predictive and Pre-symptomatic Testing: Predictive and pre-symptomatic types of testing are used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genomic disorder, but who have no features of the disorder themselves at the time of testing. Predictive testing can identify mutations that increase a person's chances of developing disorders with a genomic basis, such as certain types of cancer. Pre-symptomatic testing can determine whether a person will develop a genomic disorder, such as hemochromatosis (an

iron overload disorder), before any signs or symptoms appear. The results of predictive and pre-symptomatic testing can provide information about a person's risk of developing a specific disorder and help with making decisions about medical care.

2.8 Nature and limitations of genomic testing for complex diseases

Genomic tests for complex diseases will tell what the chances are of developing a particular genomic condition. Such results are not definitive and may leave a person wondering what to do with those results, particularly if there are therapies that limit the course of the condition.

A particular genomic test will only tell if there is specific genomic variant, or mutation; it does not guarantee that the disease will develop nor can the test provide information about other genomic diseases not being specifically looked for by that test.

At this time, most genomic tests may detect a particular problem gene but are unable to predict how severely the person carrying that gene will be affected. As with any laboratory

test, genomic tests' analytic sensitivity and specificity need to be determined before such tests are deployed for widespread use in the population. While these are straightforward, other factors relating to the clinical validity of genomic tests of complex diseases are not so straightforward. Challenges include:

1. Established gene-disease association. Reports on the association of many low penetrance genes with disease have been conflicting and clear association with disease may not be established.
2. Predictive values. These relate the sensitivity and specificity of genomic tests to the prevalence of the associated disease entity.
3. Uncertainty about risk estimation. The association between specific genes and disease outcomes is influenced by many factors including environment, epigenetics and gene-gene interactions making the ultimate contribution of identified genetic factors to overall disease risk uncertain.

Even more challenging than the validity of genomic tests is the clinical utility of tests which is based on a balance of the benefits and harms to individuals, population at large and the overall health care system. This is the realm where the ethics of genomic testing becomes an important consideration. Whereas for some major diseases like Huntington's and Alzheimer's disease, some may argue that absence of treatment is a reason for not conducting genomic tests, others would argue that conducting genomic tests that are predictive allows potential sufferers to make adequate financial and social arrangements that they may be incapable of making with onset of disease. Identification of genomic risk factors for common complex diseases such as diabetes mellitus, cancer and cardiovascular diseases may also provide strong incentive to take preventive actions and take them seriously. On the other hand, it can be argued that a negative genomic risk factor test for common complex diseases may lull

clients into forsaking proven risk reducing activities such as increased physical activity, consumption of a healthier diet and cessation of smoking. It is therefore important to study population attitudes to genomic testing for complex diseases in order to ascertain their knowledge of these tests and their expectation of the results, their understanding of the concept of risk and its application in health care.

2.9 Ethical issues in genomic testing for complex diseases

Although genetic test might be a major advance for predicting future health risks and preventive medicine, it also would raise a host of complex social and ethical issues for the patient and physician. For example:

1. Would the anxiety of living with the likelihood of one or more specific, chronic, debilitating diseases create psychological burdens that outweigh the therapeutic potential of lifestyle changes or earlier treatment due to increased vigilance?
2. If no effective interventions are known, would individuals prefer to live without knowing their genetic risk for complex diseases, or would they consider the opportunity to make social and other arrangements sufficient benefit?
3. What would individual attitudes be towards disclosure of genomic risk of complex diseases and who would they disclose to?
4. Who would individuals consider as having the right to know about their risk of genomic disease – their family members, their partner, their children or employers?
5. Should present or potential employers be aware of individual's risk of complex diseases? Should life insurance companies have access to this information?
6. When should genomic testing for complex diseases be done – as part of a medical check-up? As a child in order to identify risks and initiate early interventions?

7. Should genomic testing be tightly regulated and available only at few specialized centres accompanied by pre and post genomic testing counselling or should Direct-To-Consumer (DTC) sale of genomic tests for complex diseases be allowed?

2.10 Risks and Limitations of Genetic Testing

The physical risks associated with most genetic tests are very small, particularly for those tests that require only a blood sample or buccal smear (a procedure that samples cells from the inside surface of the cheek). Many of the risks associated with genetic testing involve the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. In some cases, genetic testing creates tension within a family because the results can reveal information about other family members in addition to the person who is tested.

The possibility of genetic discrimination in employment or insurance is also a concern. Some individuals avoid genetic testing out of fear it will affect their ability to purchase insurance or find a job.(Amy, 2008) Health insurers in Nigeria do not currently require applicants for coverage to undergo genetic testing.(Remigius, 2010:7).

The stress of planning a life on predetermined schedule could affect an individual emotionally and physically. The anxiety of living with the likelihood of one or more specific, chronic, debilitating disease create psychological burdens that outweigh the therapeutic potential of lifestyle changes or earlier treatment due to increased vigilance. Emotional burden may be placed on an individual by their physician who may not be properly trained in genetic counselling. This fact may also cause an increase in malpractice suits against physicians, because there are only very few qualified specialist in this area.

Insurance is based on the complementary principles of solidarity and equity in the face of uncertain risks. It is plausible that if insurance companies could use the results of genomic test many people would be denied vital health and life insurance. The goal of business is to make money. Selling insurance to an individual predetermined to have a genomic disorder (whether they have it or not) is not a money making proposition, because of the increased risk the company would pay out for the individuals health needs. The denial of insurance brings out the classical case of discrimination. Discrimination due to genomic composition is the loudest alarm in genomic screening debate. Genomic discrimination by insurance companies could leave millions of people without protection and cause an increased burden on the already overburdened medical insurance programs.

Social stigmatism may be placed on individuals and families because of the results of genomic tests. Along with social stigma, employers may deny jobs to individuals that are at risk for certain diseases. For example a technical field that requires a long training process may turn down a qualified applicant if they knew that the applicant had a chance of developing a debilitating disease which may limit the time when he can deploy the expensive and arduous training that has been provided. Another scenario is if an individual is screened and carries a trait that may interact negatively with the particular work environment and enhance the development of disease. The company may worry about a lawsuit being brought against them for causing the expression of the disease.

2.11 Formulating a regulatory structure of genetic tests

In addressing issues of quality in genetic testing, one must consider what it ultimately means to interpret test results accurately and fairly, and who determines the standards to which the professionals, from lab technicians to counsellors, should be held. Additionally, one must

determine how, and by whom, these standards are maintained or enforced. Indeed, these are questions to which answers are still being developed, both at national and international levels. Although many countries have recognized the need for structures to address quality assurance in genetic testing, a regulatory vacuum is widely recognized to exist particularly in developing countries.

CHAPTER THREE

3.0 RESEARCH DESIGN AND METHODOLOGY OF THE STUDY

3.1. RESEARCH DESIGN

The study design was cross-sectional and was carried out in 2 districts of Federal Capital Territory (FCT), Nigeria, 1 rural and 1 urban. Qualitative method was used for the research. We conducted 8 Focus Group Discussions (FGDs) and 27 Key Informant Interviews using agreed topic guides and prompt statements that outline general issues, the research questions and its key features.

3.2 RESEARCH SETTING

The study was done in the Nigeria Federal Capital Territory, Abuja which had a population of 778,567 in 2006 with growth rate of up to 30 per cent each year. All Nigeria's ethnic groups, tribes, and religions live there including members of the 3 major tribes - Hausa, Ibo, Yoruba and many minority ethnic groups. Muslims make up 50 percent of the population, Christians 40 percent, while the remainder adhere to indigenous beliefs. Abuja has five urban districts and several surrounding towns and villages. Asokoro (Urban) and Bwari (Rural) districts were selected for this study.

3.3 ETHICAL APPROVAL

Formal ethical approval for this study was obtained from the National Health Research Ethics Committee (NHREC).

3.4 FOCUS GROUP DISCUSSIONS (FGDs)

Four (4) FGDs were conducted in each of the 2 districts in FCT - Asokoro, and Bwari districts - (1 urban, 1 rural) making a total of 8 FGDs. FGDs were conducted separately for men and women because of religious sensitivities. Criteria for selection of participants in the FGD at each site were:

1. Literacy.
2. Age.
3. Individuals with complex diseases like hypertension, obesity or cancer and relatives.
4. Tribe and religion.

Letters were sent to participants detailing the objective of the study and inviting them to participate in the study. Each session was conducted by a moderator and a recorder while the principal investigator (PI) facilitated it. There was one pilot FGD. Copy of the FGD guide is attached as annex 1.

Table 1 below shows the categorization of participants in the FGD.

Table 1: Matrix of FGD participants' selection.

Level of Literacy	Male		Female		Total FGDs
	Youth	Adult	Youth	Adult	
Literate (Urban District)	1	1	1	1	1x4=4
Illiterate (Rural District)	1	1	1	1	1x4=4
Total	2	2	2	2	8

3.5 KEY INFORMANT INTERVIEWS

We conducted Key Informant Interviews with randomly selected health care professionals who provide care for individuals with complex diseases, selected individuals with complex diseases, relatives of people with complex diseases, religious and community leaders and opinion leaders. Tables 2 to 4 below show the distribution of categories of Key Informant Interviews that were conducted. The discussion guides were scenario-based and was updated after the FGDs to elicit more in-depth responses, using follow-up questions, prompts and probes. The Key Informant Interviews were conducted using semi-structured interview guide in the local language where necessary and addressed informants' view on genomic test in complex diseases. The Key Informant Interviews were audio-taped and lasted an average of 30 minutes, transcribed, and verified by the interviewer prior to analysis. Respondents of the Key Informant Interview survey were purposefully selected to represent a broad range of views and experiences.

Table 2: Matrix of Key Informant Interview Participants' Selection among the General Population in the 2 Districts.

Category	No of Participants per district	Total
Community leader	1	1x2districts=2
Opinion leader (male)	1	1x2districts=2
Opinion leader (Female)	1	1x2districts=2
Christian religious leader	1	1x2districts=2
Muslim religious leader	1	1x2districts=2
Traditionalist	1	1x2districts=2
Head teacher	1	1x2 districts=2

Student	1	1x2 districts=2
Total	8	16

Table 3: Matrix of Key Informant Interview Participants' Selection at Health Institutions in Urban Districts.

Category	No of Participants
Hospital Administrator/MD	1
Med Lab Scientist	1
Medical Doctor	1
Nurse	1
Pharmacist	1
Patient with a complex disease	1
Relative of patient with a complex disease	1
Total	7

Table 4: Matrix of Key Informant Interview Participants' Selection among Policy Makers at Federal Ministry of Health, Abuja.

Category	Total No of Participants	Remark
National Health Policy Maker	3	Director Health Planning and Research, Director Hospital Services and Deputy Director, laboratory services at Federal Ministry of Health(FMOH)
Ethicist	1	FMOH
Total	4	

3.6 Method of data analysis

The data was transcribed and translated to English language from the local language used for interviewing and back translated into the local language to check consistency and accuracy (In cases where interviews were conducted in local language). Information received was presented verbatim, preserving language and concept used. The analysis was done manually and no software was used.

3.7 ETHICAL CONSIDERATION

3.7.1 Informed Consent

All participants were asked to give informed consent indicating their willingness to participate in the study (Annexes 3 and 4).

3.7.2 Autonomy and Respect

Participation in the study was voluntary. All participants were intimated with the objectives of the study and informed that they are free to participate or not in the research. They were made to also understand they could withdraw their participation at any stage without any negative consequence on them as to the benefit of the research.

3.7.3 **Risk/Harm**

Efforts were made to reduce the risk of the study. Apart from the time of respondent, risks in the research were basically confidentiality and psychological injuries. The study did not identify any participant by name or any other means that can make people trace the information provided to him. Participants were assured that if it became necessary to make reference to any of them, permission to do so would be obtained from such person. Password that was used to store the data on computer was known only to the researcher. All documents

relating to the research were safely locked to prevent access by unauthorised person. All questions were asked in an un-offensive manner.

3.7.4 Justice and Fairness

Selection of participants were statistically determined and without discrimination. Every eligible person was given equal opportunity for selection.

3.8 DISSEMINATION OF RESULT OF STUDY

Paper presentations of the result have been made at the International Conference on Human Genomics in Cape Town, South Africa and Ethics and Genomic Research in Africa Conference, Abuja in March and November 2011 respectively. I also made presentation on the result at Institute of Human Virology of Nigeria in February 2011.A presentation is planned to be made in the Department of Surgery, University of Ibadan to further disseminate the result and a copy of the thesis shall be kept at the library of University of Ibadan for reference purposes. In addition the findings shall also be published in a reputable journal.

CHAPTER 4

4.0 RESULT

A total of 80 participants were interviewed for the FGD. Their ages ranged from 15 to 68 years with mean of 39.5 years and SD 20.21. There were 39 women (48.75%) and 41 men (51.25%); 20 Yoruba (25%), 20 Ibo (25%), 21 Hausa (26.25%) while 19 participants (23.75%) were from other ethnic groups. There were 38 Muslims (47.5%) and 42 Christians (52.5%). There 30 students (37.5%), 20 civil servants (25%), 15 traders (18.75%), 5 teachers (6.25%), 2 health care professionals (2.5%), 2 clergy (2.5%) and 6 from other professions (7.5%).

In the Key Informants Interviews, 15 respondents participated. Their ages ranged from 21 to 67 years with mean of 42 years and SD 13.61. There were 6 women (40%) and 9 men (60%), 5 Hausa (33.3%), 4 Ibo (26.7%), 4 Yoruba (26.7%) and 2 (13.3%) from other ethnic groups. There were 9 (60%) Christians and 6 (40%) Muslims interviewed.

4.1 Knowledge About Genomic Tests

From the FGD, most respondents did not have a good knowledge of genomic tests. Their knowledge was limited to paternity and genotype tests. For example, a participant said:

"..when a couple has a baby and there is a concern that the baby does not look like the father...when asked to do DNA test the woman might be against it...".

Similarly, most participants in KII showed limited knowledge of genomic testing. However, the result was different among health workers. This category of key informants had better knowledge of genomic tests than others. One of them said ".....genomic test reveals if an individual carries a gene which can be linked with present or future disease or behaviour....."

4.2 Regulation of genomic test

Participants in the FGD saw genomic test as a professional issue that should be done where those coming for the test can be properly counselled before and after the test. To quote a participant,

"..without a professional being involved it is not ideal to run such tests. There may also be error of interpretation of result".

They believed test result could be misinterpreted if not done by professionals. In addition patients may not have access to pre and post testing counselling.

On the other hand, a few female youths in the rural and urban centres were of the opinion that the test should be made available directly to the consumer though after proper education on how to use it. This they said will eliminate time wasted at health facilities, reduce the cost of doing the test and in addition increase accessibility to the test. One said,

"....it would be fine to test yourself to know if you have a risk of getting a disease if trained. But if more guidance is needed the person can meet with a professional at the hospital for counsel on the advantages and disadvantages. ..... So people do not go to the hospital and waste their time waiting for hours just to see a doctor for the test."

Another female respondent, a student said the test should be made available directly to the consumer for confidentiality sake"....if the test is done in the hospital or laboratory they may leak the result to a third party if it is not a good one..."

Most respondents in the KII said the test should be conducted by professionals at designated centres because the concept is new in Nigeria. "".....the concept of genomic test is still new in Nigeria and non-professionals may misinterpret the result or not be able to handle the outcome of the test..."

4.3 Relevance of Genomic Test in Nigeria

Participants in the FGD generally believed that genomic tests are relevant in Nigeria, even if there is no access to intervention that will change outcome of genetic risk. Respondents said if the tests are done, the result could inform need for life style modification, family decisions and formulation of future health plans for Nigerians by policy makers. A respondent said "It is relevant to still carry out genomic test even though the necessary intervention may not be available in Nigeria. It is better to know than not knowing like they say knowledge is power. There are other preventive measures that can be done that do not have to be medicine like a change of lifestyle".

In a similar fashion, all respondents in the KII said the test is still relevant in Nigeria even if there is no access to intervention that will change outcome of genetic risk. This they said will help an individual with an undesired result to think of what he can do to alleviate the identified problem or prevent future manifestation. A respondent said "..the test is still relevant as it helps an individual to make changes to his lifestyle where necessary...."

4.4 Willingness to do the test

All respondents in FGD were willing to do genomic tests if available. However, the willingness of the male youth participants in the urban area was subject to cost/affordability of the test, one of whom said: "..if it is not expensive, we are willing to take the test...."

In the KII, all those interviewed were also willing to do genomic tests if available in Nigeria. One interviewee said:

"....I am willing to do the test if available as it will help one to know if there is any future problem that can quickly be aborted."

4.5 Disclosure of Result to Third Parties.

Generally, the respondents in FGD expressed their unwillingness to disclose test result to a third party. However some youth participants said if their consent is sought, the result can be disclosed to partners while a few elderly respondents said they were also willing to disclose to their life insurance companies, one of whom said "....these are the people that will take care of me if I am sick, I think they should know". Participants expressed fear about disclosure of test result to employers because of the risk of losing their jobs.

In the KII most respondents said they will not want the test result disclosed to anyone except their health insurance company and their spouses. A male opinion leader in a contrary view said the test result could be disclosed to anyone or organisation that could be affected by the result of the test. Another respondent in the KII however vehemently said the test result should not be disclosed to any third party no matter the condition. He said:

"It is a confidential test....I will not want the result of the test to be disclosed to any third party under any condition."

4.6 Testing and Disclosure of Result to Children.

All participants in the FGD agreed that children can be tested to predict if they will have serious diseases in future but the result should not be disclosed to them. It was stated that children may not be able to comprehend and handle the information. In addition, the test result if unfavourable may cause irreparable emotional injury in children as they might think that was the end of life.

One respondent, a student said, "Yes children should be tested. They should not know the results as they are not the ones to take care of themselves. The parents only should know."

The KII interviewees also had no hesitation about testing children but the result should be kept from them until they are matured.

4.7 Testing Unborn Babies

Majority of the respondents in the FGD did not see any reason why unborn babies should be tested because undesirable result would lead to dilemma of what to do next. One participant said:

".... but when the results come out what will you do? Will you abort the pregnancy? The best thing is that they should not be tested as it will bring problems on what to do next when the result is not desirable."

Four of the women participants in Asokoro were of the opinion that unborn babies should be tested so that the parents can start taking precaution or evacuate the baby if the result is undesirable.

A woman said,

"It is good to test the unborn children. The earlier people know the risk of disease they are carrying the better".

Similar results were obtained in the KII as most interviewees expressed displeasure at the testing of children. A medical doctor added that the process of testing might also lead to abortions, hence he was not in support of testing unborn babies.

A few other respondents however said testing unborn babies early in pregnancy will help the mother decide if termination of the pregnancy is necessary. "...if test is done early enough, the pregnancy can be terminated if that will prevent future agony."

4.8 Effect of Religion and Culture

The FGD respondents claimed that their perception of genomic testing was not affected by religion or culture. However, a woman at the urban site said her religion only affects her view on testing unborn babies. She said:

"Not good to test the unborn because if the result is not favourable, it will result in abortion which is against my religion."

In the KII, majority of the respondents also said their perception of genomic test is not affected by religion or culture. A few individuals who participated in the KII said their religion will only affect a situation where the result of test will lead to abortion or killing of individuals with undesirable results. One said:

"....my religion will not allow me to support anything that takes life, so if genomic test will lead to abortion or killing, I am not in support".

5.0 DISCUSSION

It is notable that the participants had positive attitudes about genomic tests and potential benefits despite knowing almost nothing about the tests. They however, expressed worry over personal genomic testing, testing of unborn babies and disclosure of test results to a third party.

This study showed that most of the respondents, except a few young health workers did not have a good knowledge of genomic test. There was also a general misconception about genomic test and genotype or paternity tests. Some respondents believed that genomic tests are synonymous with paternity and genotype tests. Unlike research by Chen *et al* (2007) that indicated associations between awareness about genomic testing and socioeconomic status, gender, and age, our findings showed that the only difference in awareness was due to the medical experience of some health professionals.

In the US, geneticists, general public, consumer advocates, and governmental bodies have raised considerable alarm about Direct to Consumer Testing and the risk that consumers may be misled by false or misleading claims and may make harmful healthcare decisions on the basis of test results.(Gollust *et al,* 2003:332; Hull & Prasad, 2001:33–35). Similarly in this Nigerian study, most respondents expressed fear over personal genomic testing which they said may be misinterpreted if not handled by well trained professionals. However, younger female respondents in the FGD and KII supported out-of-hospital genomic tests because they believe these to be more confidential and avoids time wasting usually associated with hospitals/laboratories. This attitude towards genomic tests by the young women may be due to their experience of health care systems in Nigeria because women interact more with the system on account of pregnancy or because they are familiar with home based tests like those for pregnancies and have come to appreciate the ease and confidentiality involved. Similarly, Kolor *et al* (2009) in their study reported that female gender had a more positive attitude towards personal genomic tests than males.

In this study, respondents generally believed that conducting genomic tests is relevant even if there is no access to intervention that will change outcome. They emphasised that the test result could help in life style modification, family decision and formulation of future health plans for Nigerians by policy makers. This is similar to the findings of Walker, (2007) on Huntington's Disease where he reported that some respondents chose testing for Huntington's Disease despite that there is no treatment for the condition but as an aid in career and family decisions."

In this study, respondents expressed willingness to do genomic tests to predict future risk of a complex disease if asked to do so. This contrasts with result of a study of Native Americans by Bolnick *et al,* (2007) where there was a general reluctance of many Native Americans to participate in genetic research and other genetics-related activities (Tallbear, 2007:412-424). These contrasting results might be because we did not evaluate attitude to tests for specific diseases like Alzheimer and Huntington Diseases where positive result is almost getting a death sentence or differences in the historical experience of these 2 communities and their interaction with Western medical practice. Exploration of attitude to specific diseases may show a difference of attitude to doing genomic tests among Nigerians and can be explored in future research.

This study revealed that many people are sceptical about disclosure of test results to third parties. Those that agreed to disclose test results would only do it to their spouses and health insurance companies. This decision might be because of the role health insurance companies and spouses may play during sickness. Health insurance as a means of providing funding for health care is a novelty in Nigeria and there is no particularly discernible positive or negative attitude to them and their work in Nigeria at this time. This may change in future. None of the study participants agreed to disclose genomic tests results to employers because of the risk of losing job. This result substantiates the finding of Amy Harmon (2008) that some individuals avoid genetic testing out of fear it will affect their ability to find a job or keep an existing one if undesirable results are disclosed to employers. There was only one discordant voice in the KII who said the test result can be disclosed to anybody that may be affected by the outcome of the result even without his consent. This discordant voice was in line with the view of the majority of foreign jurisdictions, which were in favour of limited disclosure of genetic test results (without the consent of the patient) in cases where the harm to "at-risk" relatives is

grave and imminent and the information could result in effective intervention (Knoppers *et al* 1998:474-483).

Similar to the result obtained by Keneth *et al* (2011), "Parents viewed the benefits of pediatric testing to outweigh its risks (positive decisional balance) and were interested in pediatric testing," respondents in this study were of the opinion that children could undergo genomic tests but the result of such tests should not be disclosed to them (children) until they are mature. The reason most cited for non-disclosure of result to minors was because they are too young to comprehend and take decision on the outcome of result. Many parents thought their child might worry about a positive result, making them unlikely to enrol their child, or to choose not to tell the child test results (Bernhardt et al, 2003:315).

Most participants were against testing unborn babies because of the risk of harming the foetus and the dilemma of what to do next if the result is unfavourable. A study conducted by Thomas (2007), showed that there is a strong religious influence on attitudes and approaches towards genomic test testing. In contrast, our respondents claimed that religion and culture did not affect their attitude to genomic testing, except where its outcome may suggest action that contradicts their beliefs and practices. For example if testing an unborn child raises questions about abortion.

Limitations of the Study

The study was limited by the use of only qualitative methods but the findings lay a foundation for more research using other methods to further probe the responses obtained. In addition, the study was restricted to Abuja, Nigeria's capital. Even though Abuja is a cosmopolitan city with different Nigerian tribes, yet conducting the study in different parts of the country may reveal different results.

ANNEX 1

Focus Group Discussion Guide

Background

Thank you for agreeing to participate in this discussion group. I am interested in learning about your beliefs and opinions about genomic test in complex diseases.

A genomic test is the analysis of human genetic make in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. It reveals if an individual is carrying any future risk of a disease.

Complex diseases are those caused by a combination of genetic, environmental, and lifestyle factors. These diseases include hypertension, diabetes mellitus, metabolic syndrome, cancers, mental health diseases, autoimmune diseases etc.

I will like to hear what you think about this issue so please feel free to express your views even if you disagree with the general view. All comments whether negative or positive are important. The discussion will be recorded so that none of your comments are omitted and a report will be prepared from the transcripts, but the report will not identify anyone by name. Every effort will be made to keep your personal information confidential.

Opening Statement

In genomic testing for low penetrance genes and complex diseases, the genetic tests reveal only that individuals carry a risk. Often this risk is very low – 2 – 5% and needs to be combined with other risk factors (genetic and environmental) for diseases to occur.

1. What do participants know about genomic testing and its state today?

2. Given the opening statement above, what is their view about regulation of genomic tests? Should genomic test be tightly regulated and be available only at special facilities with pre and post testing counselling or available directly to consumer.
3. What is their view on the relevance of genomic test in Nigeria considering the fact that there may be no access to intervention that will change outcome of genetic risk.
4. If genomic test is available how will they feel?(Will they allow themselves or family members to undergo genomic test for complex diseases)
5. What is their attitude towards disclosure of result of genomic test for complex diseases to a third party (Will they want their future partners, employers, potential employers or life insurance companies to have access to the result)
6. Should children be tested so that we can predict if they will have serious diseases in future? If they are tested should they be told the result, if not, why not?
7. What is your view about testing unborn babies to predict if they will have future serious diseases?
8. How has religious or cultural background affected their perception on conducting genomic test that reveals future risk for a serious disease?

ANNEX 2

Key Informant Interview Guide

Background

Thank you for agreeing to participate in this interview. We are interested in learning about your belief and opinion about genomic test in complex diseases.

A genomic test is the analysis of human genetic make in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.It reveals if an individual is carrying any future risk of a disease.

Complex diseases are those caused by a combination of genetic, environmental, and lifestyle factors. These diseases include hypertension, diabetes mellitus, metabolic syndrome, cancers, mental health diseases, autoimmune diseases etc.

I will like to hear what you thinkabout this issue so please feel free to express your views even if you disagree with the general view. All comments whether negative or positive are important. The discussion will be recorded so that none of your comments are omitted and a report will be prepared from the transcripts, but the report will not identify anyone by name. Every effort will be made to keep your personal information confidential.

Start with warm up questions.

In genomic testing for low penetrance genes and complex diseases, the genetic tests reveal only that individuals carry a risk. Often this risk is very low – 2 – 5% and needs to be combined with other risk factors (genetic and environmental) for diseases to occur.

1. What do you know about genomic testing and its state today?

2. Given the opening statement above, what is your view about regulation of genomic tests? Should genomic test be tightly regulated and be available only at special facilities with pre and post testing counselling or available directly to consumer.

3. What is your view on the relevance of genomic test in Nigeria considering the fact that there may be no access to intervention that will change outcome of genetic risk.

4. If genomic test is available how will you feel?(Will you allow yourself or family members to undergo genomic test for complex diseases)

5. What is your attitude towards disclosure of result of genomic test for complex diseases to a third party (Will you want your future partners, employers, potential employers or life insurance companies to have access to the result)

6. Should children be tested so that we can predict if they will have serious diseases in future? If they are tested should you be told the result, if not, why not?

7. What is your view about testing unborn babies to predict if they will have future serious diseases?

8. How has religious or cultural background affected your perception on conducting genomic test that reveals future risk for a serious disease?

Annex 3

INFORMED CONSENT FOR FGD ON KNOWLEDGE, ATTITUDE AND PRACTICES OF NIGERIANS TOWARDS GENOMIC TESTS IN COMPLEX DISEASES.

This statement was read out at the beginning of the FGD and individuals were made to understand that staying to participate in the FGD was indicative of consent.

This is an explorative study to examine the knowledge, attitudes and practice of Nigerians towards genomic tests in complex diseases and to identify how the knowledge, attitudes and practice correlate with gender, age, religion, education and related factors.

Genomic test is the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.

Complex diseases are caused by a combination of genomic, environmental, and lifestyle factors. These diseases include hypertension, diabetes mellitus, metabolic syndrome, cancers, mental health diseases, autoimmune diseases etc.

The study is qualitative but may involve the risk of confidentiality and psychological injuries due to the nature of some questions. However, it has been designed in a way that you will not be identified by name or any identification that will be traceable to you. Codes will be used to identify participants on the questionnaire. If it becomes necessary to make reference to you, permission to do so will be obtained from you. Password that is known to only the researcher and data analyst will be used to store the data on computer. All documents relating to the

research will be safely locked to prevent access by unauthorised person. All questions will be asked in an un-offensive manner.

Participation in this study is voluntary. You are free to respond or not respond to any or all of the questions. You can withdraw your participation at any stage without any negative consequence on you as to the benefit of the research.

You may not benefit directly from the outcome of this study but the result will be used to develop educational and policy interventions on genomic test which will benefit many in this community and beyond.

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE:_____SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the investigator to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____SIGNATURE: _____

NAME: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

(Your name is for the purpose of consent only and will not be linked to your responses in the discussion. Moreover, the consent form does not have your demographic information which makes it difficult to trace the name to you. The form will also be kept under lock and key and only be accessible to the principal investigator)

In case you need further clarifications, please contact:

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Annex 4: Consent to participate in Key Informant Interview

INFORMED CONSENT FOR KEY INFORMANT INTERVIEW ON KNOWLEDGE, ATTITUDE AND PRACTICES OF NIGERIANS TOWARDS GENOMIC TESTS IN COMPLEX DISEASES.

This statement was read out at the beginning of the interview and individuals were made to understand that staying to participate in the interview was indicative of consent.

This is an explorative study to examine the knowledge, attitudes and practice of Nigerians towards genomic tests in complex diseases and to identify how the knowledge, attitudes and practice correlate with gender, age, religion, education and related factors.

Genomic test is the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.

Complex diseases are caused by a combination of genomic, environmental, and lifestyle factors. These diseases include hypertension, diabetes mellitus, metabolic syndrome, cancers, mental health diseases, autoimmune diseases etc.

The study is qualitative but may involve the risk of confidentiality and psychological injuries due to the nature of some questions. However, it has been designed in a way that you will not be identified by name or any identification that will be traceable to you. Codes will be used to identify participants on the questionnaire. If it becomes necessary to make reference to you, permission to do so will be obtained from you. Password that is known to only the researcher and data analyst will be used to store the data on computer. All documents relating to the

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You may not benefit directly from the outcome of this study but the result will be used to develop educational and policy interventions on genomic test which will benefit many in this community and beyond.

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE:_____SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the investigator to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____SIGNATURE: _____

NAME: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

(Your name is for the purpose of consent only and will not be linked to your responses in the discussion. Moreover, the consent form does not have your demographic information which makes it difficult to trace the name to u. The form will also be kept under lock and key and only be accessible to the principal investigator)

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