Managing Incidental Findings in Genomic Research: A Systematic Review and Hermeneutic Exploration

BY

OLUKUNLE CORNELIUS EWUOSO

(Matric. No. 173197)

Being a dissertation submitted to the Department of Surgery, Faculty of Clinical Sciences, College of Medicine, University of Ibadan, Nigeria, in partial fulfillment of the requirement for the award of Master of Science Degree in Bioethics (M Sc.)

BTH 777

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CERTIFICATION

This is to certify that the dissertation titled: *Managing Incidental Findings in Genomic Research: A Systematic Review and Hermeneutic Exploration,* submitted to the Department of Surgery (Bioethics), University of Ibadan, Nigeria, for the award of the degree of Masters of Science in Bioethics of the University of Ibadan, is an original research carried out by CORNELIUS OLUKUNLE EWUOSO.

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DEDICATION

This essay is dedicated to all researchers who in silent tears, engage in the tedious task of tidy thinking.

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Abstract

The advent of genomics has greatly improved and revolutionized medicine. One key word describes this revolution: information-empowerment. This is directed to two ends: predictive and preventive. Information-empowerment has changed medicine, yet it also poses the greatest threat to its survival, especially when the information is not directly intended. There may be an emerging consensus that valid and clinically significant incidental findings should be returned to subjects; this emerging consensus is not supported by any systematic review nor have the scientists' and other stakeholders' attitudes and current practices been organized. Future directions are equally missing. In addition, ethical, legal and social implications of this emerging consensus, have not been carefully considered. These are significant gaps.

To assess this consensus, a literature search was carried out between the 20th and 23rd of October, 2013, using PubMed search engine and in Genetics in Medicine website. Using a combination of unique phrases, such as 'incidental findings genomic research', 'return incidental findings', etc., and certain filters, 19 articles were selected. These articles were reviewed using descriptive method. Our review confirms a majority support that findings with serious health condition (68.42%) or clinically actionable (68.42%) should be returned. This review also questions whether this support can be called a consensus. Our result shows that the support represents views of Northern Americans (USA 84.2% and Canada 15.8%). Critical contributions of Africans, Asians and Europeans are missing in this discourse. We, therefore, recommend that studies should be carried out in these continents.

Hermeneutic (phenomenological) exploration was useful in helping us understand the historicality behind the willingness to return incidental findings. This was situated within the locale of the desire to protect human subjects from abuse. This method was also useful in gaining insights into the implications of creating an obligation whereby researchers routinely return research (incidental) results. This, we argued, would distract researchers from research aim and objectives or stifle research progress. Hence, hermeneutic (phenomenological) method cautions us against obliging researchers to return incidental findings. They may, however, be encouraged to do so if this would not distract them from their research aim and objectives.

Keywords: Genomic Research, techniques, incidental findings, hermeneutics, systematic review.

Introduction

01 Background

Technology has soared to the stratosphere. It is changing the way we do things. Advancement in technology is also changing the way medicine is being practiced. The thinking, today, is that medicine needs to be more proactive than re-active. As a result, medicine is going the way of genomics. Defined simply, Genomic medicine is a 'discipline in genetics, which relates recombinant DNA, DNA sequencing methods and bio-information to organize assemble, analyze the function and structure of genomes'(Guttmacher & Collins, 2002). All living things have genomes which contain the biological information needed to keep and build the life of the living thing. Genomics is the study of these genomes, its functions and interactions with all the genes in the genome (Khoury, 2003).

It is well established in literatures that genetic risk is a major component of many health conditions Each gene is made up of DNA. Scientists study this DNA in order to discover, albeit in varying degrees, not only what genes may predispose a person to certain health anomalies, but how genes that are related to diseases and health are passed along hereditary lines. The different genes connected to diseases are also studied, in order to better understand the functions of defective genes or produce drugs to treat the illnesses associated with them.

In certain cases, genetic information has significantly empowered physicians in clinics to put in place preventive measures that significantly reduce the probability of the disease occurring in at risk individual.

Today, with many studies confirming the reality that genomic research has introduced novel advancement in the healthcare deliveries around the world, one can reasonably assert that humanity has taken a 'giant step in her conquest of nature'. However, this landmark advancement, has also heralded serious far reaching and complex issues. Some of these issues are social in nature, others are ethical and legal. Some of the ethical issues include challenges to notions of informed consent, privacy, confidentiality, autonomy, data sharing, data security, genetic discrimination, stigmatization, benefits, risks, disposition and use of data by third party researcher, role of community consultation and engagement, and compensation to sample and data providers within genomic research. Legal issues include intellectual property, ownership, liability, the duty to warn, the right to know, and non-medical use of genomics in non-health care settings for employment

and arbitrating in criminal or civil courts. Finally, social issues include blurred distinction between genomic research and treatment, implications of availability of genetic information for the society, the impact of genetic variation research on understanding race and relationships within human populations. No issue, however, is raising more contentions, and posing real difficulties than that of incidental findings during genomic research.

02 Statement of Problem

There is no denying the fact that genomics is redefining medicine in a whole new way. One key word describes the radical transformation which genomics is causing in medicine: Information-empowerment. This is directed at a two-fold end: predictive and preventive. Genomics is empowering physicians to find genetic alterations that make individuals susceptible to certain diseases such as cancer, diabetes or Down's syndrome. This novel endeavor has also offered humans the prospects of one day having treatment designed to help individuals overcome health anomalies. The extent of information that could be generated, using different technologies and methods, is unquantifiable.

Information-empowerment has been the greatest gain of genomics, yet it also poses the greatest threat to the survival of genomic research, especially when the information is incidental. An incidental or ancillary finding is an information not directly intended and often beyond the scope of the study. Our examination of existing literatures shows that:

a) The full ethical, legal, and social implications of ancillary or incidental findings for researchers and other stakeholders have not been clearly and intelligently synthesized.

b) There is need to carefully reflect on the negative and positive implications of returning incidental findings to participants.

c) While there appears to be an emerging consensus that valid and clinically significant incidental findings should be returned to participants, this emerging consensus has not been supported by any systematic review nor have the scientists' and other stakeholders' attitudes and current practice, been organized.

d) The reasons provided for the consensus, have also not been carefully synthesized into a whole.

e) The opinions of scientists on 'who should return incidental findings: genetic counselors, researchers or other medical personnel', also need to be systematically reviewed and analyzed.

f) The views of participants, since they are directly affected by these incidental findings, equally need to be synthesized.

g) Future directions, on the effective management of ancillary or incidental findings in genomic research are missing.

These gaps are significant, since the current techniques and future technologies used in genomic research would continue to yield massive information, and some would be incidental. This study would contribute to bringing these gaps, by systematically examining emerging consensus and attitudes toward ancillary or incidental findings, exploring ethical, legal and social implications of the same and highlighting future directions, by making recommendations for future studies.

The blurred distinction between research and treatment, conflict between benefits to research participants and the scientist's duty to produce valid and generalizable study results, respecting participants' autonomy and rights not to know, create unique ethical dilemmas for scientists' management of incidental findings. Unique issues may also arise in retuning incidental findings to special population such as pregnant women following prenatal diagnosis, relatives of deceased participants and participants lacking capacity. Incidental findings, particularly those predictive of future illnesses may also create anxiety in participants and families, cause psychological harm to relatives and third parties. Breach of trust, respect for participants' privacy, the duty to warn versus right to not/know, may equally create legal issues in incidental findings management.

Furthermore, there is a raging debate amongst researchers on what incidental findings should be returned, and who should return it. This debate has left researchers in a state of quandary on how to deal with incidental findings. This study would carefully reflect on this debate,

systematically organize the thoughts of scientists and other stakeholders on these vexing issues, highlight future directions and thus, fill the identified gaps.

03 Aim and Objectives

The aim of this study is to explore the complex issues raised by the finding of incidental findings in genomic research. Specifically, we would:

i. Examine the concept, objectives and techniques of genomic medicine/research
ii. Discuss some challenges of incidental findings in genomic research
iii. Explore the debate and controversies on incidental findings management
iv. Carefully reflect on the debate about who should return incidental findings
v. Systematically review emerging attitudes, perspectives, views and consensus on incidental findings
vi. Make recommendations to mitigate the identified legal, social and ethical issues involved in incidental findings management
vii. Make recommendations for future studies

CHAPTER 1.

LITERATURE REVIEW

Genomic research has raised an avalanche of important and far reaching questions, a significant part of which border on information management. Studies on information management in genomic research indicate that management of incidental findings raise significant ethical concerns. This is especially the case because of the technologies and methods employed in genomic research. These technologies will significantly impact genomic research by way of massive information generation. Some would be directly related to the study, while other information would be incidental. Susan Wolf and colleagues (2008b) articulate this point well in the following statement: "the technologies used in research to generate images, scans, and data can now produce so much information that there is significant potential for incidental findings, findings generated in the course of research but beyond the aims of the study". As Lohn and colleagues (2013) stretch this argument further when they remarked that full disclosure and non-disclosure policies may not be the best approach in handling incidental findings in genomic research. Full disclosure may not be feasible in some cases, financially burdensome, physically impossible and may slow down the progress of scientific research. Again, non-disclosure may equally not be legally and ethically defensible, especially if these incidental findings have serious clinical significance.

In order to comprehend the taxonomy of questions raised by incidental findings, it is imperative we define genomic research: the concept and science, as well as explain the present technologies and methods employed in genomic research.

1.1 Genomic Medicine and Research

At its core, genomics, "as a term coined only 15 years ago, is the study not just of single genes, but of the functions and interactions of all the genes in the genome"(Guttmacher & Collins, 2002). This is distinct from genetics which studies a single gene and its effects. Genomics embraces a broader sphere than does genetics. Peter Byers (2006) articulates this point well in his article, "The Role of Genomics in Medicine- Past, Present and Future." In his words:

> The objective of genomics is to determine the genetic bases of those differences in response to environmental agents, including medications, and differences that may predispose to the development of common and potentially personally devastating and societal expensive disorders, and to use them in populations to thwart adverse response, increase the frequency of beneficial response, and intervene to prevent or delay the onset of disease.

The application of the science of genomics in medicine rests on direct experimental access to the entire genome and applies this knowledge to effective management or prevention of common conditions, such as breast cancer and colorectal cancer, human immunodeficiency virus (HIV) infection, tuberculosis, Parkinson's disease, and Alzheimer's disease.

1.1.1 History of Genomic Research

Historians like to attribute the beginnings of genomic research to 19th century monk Gregor Mendel, who is also called the father of genetics. Mendel was the first to conduct experiments on transmission of certain hereditary traits in plants and flowers, such as white or red, tall or short. Mendel distinguished two types of hereditary patterns: recessive and dominant. The hereditary traits themselves do not mix or blend; they are transmitted in discrete units, which he called 'factors'. Today, these factors are known as genes (Delude, 2003).

Mendel's article, "Experiment on Plant Hybridization" where he described his findings, received little attention until 1900 when some scientists realized that the dominant and recessive patterns discribed by Mendel also applied to some genetic diseases such as Huntington disease, cystic fibrosis and sickle cell anemia. This realization stimulated a number of studies in the newly formed field of genetics, both in England and the United States. Scientists, beginning with Hermann Joseph Muller in 1926, began to 'associate the inheritance with chromosomes and to find models predominantly in fruit flies, thus building on the initial foundation laid by Mendel'(King et al., 2006). Mendel had explained how some diseases are inherited, but it was Muller who first discovered how the disease gene came to be in the first place. From exposing fruit flies to x-rays and observing how their offspring developed deformities, Muller confirmed that 'genes can be chemically changed or mutated, and those genetic mutations can cause physical changes'(Delude, 2003). A gene is a long, monotonously repetitive molecule called deoxyribonucleic acid (DNA).

Oswald Avery proved that DNA contains a coded language for genetic information. Scientists then found out that variations in this code can alter the way a gene works. They intuited

that sequencing the human DNA would improve knowledge about genes and their functions. Sequencing genes started in 1970s but the process was quite challenging and it was difficult to imagine, tackling the lengthy, repetitive strands of DNA that constitute whole genome. In 1990, the United States' National Institute of Health and Department of Energy commenced an initiative to sequence the entire human genome led by famous researchers such as Watson, Collins, and Sulston. This was complemented by a private initiative led by Craig Venter of the Institute for Genomic Research (TIGR). This project was named the Human Genome Project (HGP)(Delude, 2003). This project, which was completed in April 2003, has given scientists the ability, for the first time, to read nature's complete genetic blueprint for building a human being.

We now believe that human beings have between 19,000 and 25,000 genes, and that several genetic and epigenetic factors are responsible for human complexity. However, the prohibitive cost and complexity of the human genome led to development of techniques that enable studies of gene-disease association at lower cost such as the International Haplotype Mapping project (the HapMap). HapMap project was based on the premise that genes tend to be inherited in blocks of closely associated genes. The outcome of the HapMap project is the implementation of thousands of Genome-Wide Association Studies (GWAS) which have enabled a large number of gene-disease association, pharmacogenomics and population studies.

Today, the cost of sequencing human genome has been greatly reduced. Owing to second-generation technologies such as Illumina, and AB SOLiD, tens of millions of DNA sequence reads can become available. The second generation methods largely apply to genome sequencing, epigenome characterization, genome resequencing and DNA-protein interactions, As observed by Thudi and colleagues (2012) these second generation technologies are being utilized for *de novo* sequencing, whole genome and transcriptome analysis. The emergence of these second-generation technologies has helped scientists in increasing accuracy and throughputs thus, further driving down cost. However, owing to the challenges these high-throughputs have for data storage and transfer (Thudi et al., 2012), scientists are working hard to make third generation sequencing technologies such as single-molecule technologies (SMS) available. These technologies can generate longer sequence reads in higher throughputs, with higher accuracy and in a relatively short time. Scientists are optimistic that in few years, genotyping by sequencing would soon become a routine feature of human life.

1.1.2 Scope of Genomic Research

Discovering the human genome was the first step in the genomic research on how information coded in DNA may lead to the prevention of health anomalies. The next stage of genomic research is to meaningfully tap the knowledge provided by this information.

The broad areas of genomic research include the following:

i. genetic testing
ii. gene therapy
iii. reproductive genomics
iv. pharmacogenomics

1.2 General Methods and Technologies for Genomic Research

Technologies used in genomic research have undergone significant rapid advancement in the last few decades; delivering more information, leading to new knowledge, and increasing our understanding of how our cells function and diseases develop.

Some basic methods and technologies used in genomic research include genome sequencing, genome-wide association studies, gene expression analysis and epigenetics, and bioinformatics. These cutting-edge technologies and methods are daily increasing human power to navigate the complex DNA structure, causing novel breakthroughs in the study of diseases, and greatly impacting treatment plans of the same.

1.2.1 Genome Sequencing

Genome sequencing is the process of determining the precise order of nucleotides within a DNA molecule. It includes any method or technology that is used to determine the order of the four bases – adenine, guanine, cytosine, and thymine – in a strand of DNA. The DNA base matching allows scientists to systematically organize sequence of gene segments, whole genes, chromosomes and, the complete human genome), to ultrafast DNA sequencing; some of them still under development. Examples of these ultrafast DNA sequencing include sequencing-by-hybridization (SBH), nanopore sequencing, and sequencing-by-synthesis (SBS).

Franca and others have identified four general methods, in the evolution of genomic sequencing technologies. They include the Sanger method; the Maxam & Gilbert method; the Pyrosequencing method; and single molecule sequencing (Franca et al., 2002).

1.2.1.1 Sanger Method

This method may also be referred to as ‘dideoxy sequencing’ or ‘chain termination’. In simple terms, Sanger method, created by Frederick Sanger and colleagues in the 1970s, is the sequencing of DNA which employs an enzyme that has the capability to polymerize DNA and label nucleotides.

As described by Adams (2008), the Sanger method ‘involves using a purified DNA polymerase enzyme to synthesize DNA chains of varying lengths’ (Adams, 2008). A basic feature of this method is the inclusion of dideoxynucleotide triphosphates. These are chain terminating dideoxynucleotides which lack 3' hydroxyl (OH), to inhibit further strand extension. The effect of this inhibition is a number of DNA fragments of varying lengths. These are, afterwards, distinguished from each other by size, and by means of a method in which an electric field pulls molecules across a gel substrate or hair-like capillary fiber (Adams, 2008).

In more technical terms, the Sanger method combines four parallel sequencing reactions to sequence a single sample. Each reaction is made up of single-stranded template, a specific primer to start the reaction, the four standard deoxynucleotides (dATP, dGTP, dCTP, and dTTP), and DNA polymerase. These features are used to prevent the chain from terminating in the same nucleotides, and to make the DNA sequence simple to read, for the scientists. Some areas of application include mutation analysis, plasmid sequencing, amplicon analysis and targeted genomic DNA sequencing

1.2.1.2 Maxam & Gilbert method

Maxam and Gilbert method was developed by Allan Maxam and Walter Gilbert in 1976. In simple language, this method employs nucleobase-specific partial chemical modification of DNA. As Franca and others explained, the main features of Maxam/Gilbert method are the chemical reactions. Two different groups are observable; the first group is a four-lane method, where four separate cleavage procedures are used, and the information is displayed in four parallel gel lanes. The second group is a one-lane method, where all reactions are based on only one chemical modification and the information is displayed in one gel lane (Franca et al., 2002).

One advantage of Maxam/Gilbert method is that, unlike the Sanger method, it allows the sequencing of a fragment from the original DNA fragment, less susceptible to mistakes and can

easily be controlled, since it gives a clear chemical distinction between bases. This method has been adopted in the past, to analyze DNA-protein interactions, to detect point mutations and to sequence short DNA fragments. There are other disadvantages, as pointed out by Franca and others; the chemical reactions are slow, and there is also prevalence of incomplete reactions. This may decrease the read-lengths (Franca et al., 2002).

1.2.1.3 Next Generation Method

Next generation methods have been necessitated by the need to reduce sequencing cost, increase high-throughputs and safe time. Some of them include Pyrosequencing, polony sequencing, DNA nanoball sequencing, single molecule real time (SMRT) sequencing, SOLiD sequencing, to mention a few. For the purpose of this section, we would discuss only two of them; pyrosequencing and single molecule real time (SMRT) sequencing.

1.2.1.3.1 The Pyrosequencing Method

This is an efficient, low cost method of DNA sequencing, based on the detection of pyrophosphate released following the incorporation of nucleotide into DNA chain by DNA polymerase. As Lin and others explained (Lin et al., 2010):

Instead of using 3′-modified dNTPs to terminate DNA polymerization, Pyrosequencing adds dNTP bases one at a time in limiting amounts to control DNA synthesis. The dNTPs are dispensed in a specific order. DNA polymerase extends the primer while the complementary dNTP is added and pauses when it encounters a noncomplementary base. The reinitiation of DNA synthesis follows the addition of the next complementary dNTP. As a nonfluorescence technique, Pyrosequencing measures the release of inorganic pyrophosphate, which is proportionally transformed into visible light by a cascade of enzymatic reactions. The generated light is recorded as a series of peaks called a pyrogram, which represents the order of complementary dNTPs and implies the underlying DNA sequence.

Pyrosequencing has broad application for SNP genotyping, identification of bacteria, fungal detection, *de* novo sequencing, mutation detection DNA methylation analysis, microbial and viral typing, high-throughput re-sequencing and recommended for allele frequency studies.

1.2.1.3.2 Single Molecule Real Time Sequencing

This is also a next generation method, albeit considered by some scholars (Thudi et al., 2012) properly belong to the third generation method. This method is asequencing by synthesis approach and it involves synthesizing DNA in zero-mode wave guides. The sequencing is performed by using unmodified polymerase and fluorescently labeled nucleotides flowing in the buffer stream. The labeled DNA is then attached onto a microsphere. The streams are such that only the florescence occurring by the bottom of the well is detected. The labeled florescent is then detached from the nucleotide, after its incorporation into the DNA strand, thus leaving an unmodified DNA strand. This method allows detection of nucleotide modification, as well as reads of 20,000 nucleotides or more. (Lin et al., 2010).

Single molecule sequencing can be used for a broad range of genomic research, which include *De novo* genome sequencing, in-vitro diagnostic, re-sequencing, and methylation detection.

1.2.2 Genome-Wide Association Studies

Genome-wide association study is a method of mapping out common genetic variants associated with particular disease conditions. This method proceeds by identifying the frequency of single nucleotide polymorphisms (SNPs), in people with a disease or particular trait, and compares it with people without the disease or trait. The knowledge from this study may then be used to pinpoint genes that may be associated with the disease.

Since genome-wide association studies are concerned with identifying common disease variations across human genome, these studies have contributed to the understanding of genetic variations associated with diseases, as well as variations which may influence an individual's drug response. This appears to be Stranger and colleagues' point (2011), when they argued that genome-wide study is hypothesis-generating study, systematically prioritizing genes or genomic regions for further investigation, while providing an overall description of genetic architecture: estimating heritability, the number of loci underlying phenotypic variation, and the distribution of effect sizes, as well as suggesting whether genetic interactions among loci or among traits exists (Stranger et al., 2011).

At the moment, this method has been able to identify the genetic variations associated with complex disease conditions such as diabetes, heart abnormalities, Crohn's and Parkinson disease

(Stranger et al., 2011). Association, however, does not mean causation. These associations also need to be replicated in independent samples in often larger and different populations, in order to strengthen the validity of genome-wide studies. In the future, these genome-wide association studies, some scientists believe, would greatly impact healthcare delivery by empowering physicians with information to deliver personalized medicine, tailored to each person's unique genetic makeup, hence opening new horizons for the development of therapeutic interventions.

Today, as far as our knowledge could reach, genome-wide studies are carried out in two groups (one group with a particular disease and the other serving as control). Stranger and others are optimistic that DNA sequencing will be 'a key feature of future genome-wide studies, through candidate locus resequencing in large cohorts, whole-exome sequencing, and eventually whole-genome sequencing of large numbers of individuals' (Stranger et al., 2011). Genetic Testing and Pharmacogenomics, remain two broad areas where genome-wide association has been employed.

1.2.3 Gene Expression Analysis and Epigenetics

Gene expression is the process where the information from a gene is used in the synthesis of a functional gene product Every DNA contains the genetic information of any individual. Human genes are divided into exons and introns. The exons alone carry information required for protein synthesis. This genetic information is first copied to a molecule called messenger RNA (mRNA), which is the first stage of gene expression. The mRNA are subsequently processed by splicing to remove intron sequences, and to create a mature mRNA. This mRNA then makes a journey to the cytoplasm, where they participate in protein synthesis, which is the second stage of gene expression, by specifying the particular amino acids that make up individual proteins.

However, it would be instructive to note that all genes in the human genome are not expressed in the same way. Nonetheless, all genes are surrounded by DNA sequences which influence their expression. Proteins also known as transcription factors are associated with these sequences, and can switch the genes on or off. An analysis or profiling may then be carried out to determine the pattern of genes expression, at this stage of genetic transcription, usually under specific condition or in a particular cell. Gene expression may be controlled through the chemical modification, often methylation, of the DNA without changing the DNA base sequence. The study of methylation is referred to as epigenetics. Epigenetic analysis complements DNA sequencing, genome-wide association analysis, and gene expression analysis. In sum, these techniques are intrinsic in helping

scientists gain an understanding of how DNA changes and gene expression interact in the disease process.

1.2.4 Bioinformatics

Bioinformatics adapt knowledge from areas of computer science, mathematics and engineering, to generate complex software and tools which are subsequently used to store, retrieve, organize and analyze biological data. Within the context of genomic research, bioinformatics provide algorithms and applications for cutting-edge sequencing technology, microarray analysis, mass spectrometry, and gene ontology, which are used to read, analyze and organize genomic and proteomic data.

One key feature of bioinformatics is the use of complex machines to analyze genetic information so as to understand human diseases, and identify new molecular targets for drug discovery. These machines have great potentials for generating massive amount of data from any human genome. Bioinformatics is also uniquely distinct from other methods and technologies of genomic research because of its focus on developing and applying computationally intensive techniques to achieve this goal. Today, bioinformatics is revolutionizing science through its power to generate information. It is widely employed in the different areas of genomic research including gene finding, genome assembly, drug discover and design, genetic testing, protein structure alignment and prediction, genome-wide association studies, etc.

In sum, the sophisticated technologies and methods employed in genomic research have significantly impacted and revolutionize science with their capacity to generate massive amounts of information. With these technologies, the potentials for stumbling upon clinically actionable information have also overwhelmingly increased. Genome and exome sequencing, using massively parallel technologies can uncover genetic variants, some of which would be unrelated to the study (Lohn et al., 2013, Johnston et al., 2012). Neuro-imaging scans, Wolf and others equally add, can now visualize the entire human head; genetic studies too, may reveal, sometimes unwanted information such as misattributed paternity (Wolf et al., 2008b).

The continued use of these technologies, in genomic research, would only raise more far reaching and complex questions about how this information would be handled, especially when they are incidental. Current practice has not been reviewed, neither has a synthesis of existing studies on attitudes and perspectives of stakeholders toward incidental findings, been carried out.

This is now an imperative. A study in the past (Steinsbekk & Solberg, 2012), has attempted to achieve this feat, however, issues generated by incidental findings were not clearly and lucidly distinguished from issues raised by return of individual results. Instead, the authors lumped the two issues together. A critical synthesis of the views of scientists' on incidental findings, and current practice, is still lacking in the academia. This study would fulfill this task.

1.3 General Issues on Information Management in Genomic Research

There are several issues which information emanating from genomic research may trigger. They include issues of informed consent, privacy and confidentiality. Genomic research can lead to an early detection of health anomalies, and provide valuable information for the scientific community.

1.3.1 Legal Issues

The principal legal issues which arise include intellectual property issues, ownership and liability issues, genetic discrimination and stigmatization, the duty to warn and the right to know. Questions have also been raised regarding the conflict between a researcher's obligation to respect private genetic information and the potential legal liabilities resulting from the failure to disclose information, especially if this information has clinical significance. For example a pregnant woman takes part in a genomic research to test if her fetus has any trait of Down's syndrome. The test revealed that the fetus has Down's syndrome. During the course of analysis of genomic data, the researcher also discovers that the woman carries a risk for BRCA 1 and BRCA 2 later in life if she lives long enough. This is an incidental finding which the researcher knows would significantly benefit the participant. Yet it is not clearly indicated in the consent form that she would like to be told. So how should the researcher manage this?

Some have suggested that if the information would benefit the health of the participant and improve their well-being, then it should be disclosed. There are, however, cases where disclosing the incidental finding could also lead family members to embrace lifestyles which may put them at great risk. In a case presentation by Fulda and Lydens;

> A 55 year old female dialysis patient who was identified as a carrier of a dominant genetic disorder: autosomal dominant polycystic kidney disease (ADPKD). She had four sons who underwent screening and were identified as carriers. One of her sons was 32 years old and the father of a six year old when he first developed symptoms of ADPKD. He committed suicide. Another son, who was 30 years old, divorced his wife and sold their home to keep from burdening her or planning a family. He did not have problems until he was 54. A third son was 25 and left his fiancée for the same reason. He later died from another cause without having ever developed symptoms. The fourth son was 21 when identified as a carrier of ADPKD. He quit school and took a good paying job to live life to the fullest. He also never married. At the time of the article's publication, he was 42 and had never experienced symptoms(Fulda & Lykens, 2006).

This family demonstrates how knowing of a genetic disorder causes people to make life altering decisions. If the disorder had not been disclosed to them, they might have lived much happier lives. But not disclosing too, has its own legal implications, as in the case of *Greco V. United States.*

In *Greco v. United States,* Sunni Greco sued some Air Force Doctors for negligence in her prenatal care and delivery because they negligently failed to make a timely diagnosis of physical defects and anomalies afflicting her child when it was still in the mother's womb. Because of this, it denied Sunni an opportunity to terminate her pregnancy and thereby caused damages to attendant to the avoidable birth of an unwanted and severely deformed child. The judges ruled in her favor, and said that she has a case to sue doctors for malpractice (Greco v. United States, 1995). In conclusion, different countries have different guidelines for dealing with ancillary medical information. Usually these guidelines are developed from court proceedings, administrative and regulatory laws. These would be further explored in the second chapter.

1.3.2 Social Issues

The principal social issues include blurred distinction between genomic research and treatment, and implications of genetic information for the society. Confidentiality, privacy and security of genetic information may equally raise far reaching social questions. Existing literatures have explored these issues. Our principal focus is to explore the issues raised by incidental findings, as well as scientists and other stakeholders' attitudes to the same. We would also make recommendation at the end of the study. Suffice to say at this point that one critical way of

mitigating these issues would be a radical rethinking of the way researchers obtain informed consent. It is important that prior to any research endeavor, the researcher discusses with the participants before obtaining consent:

i. Risks, limitations, and benefits of testing or not testing
ii. Alternatives to genetic testing
iii. Details of the testing process
iv. Privacy/confidentiality of test results
v. The voluntary nature of testing
vi. Potential consequences related to results, including: (1) impact on health; (2) emotional and psychological reactions; (3) treatment/prevention options; and (4) ramifications for the family
vii. Possibility of finding other conditions not being tested
viii. Whether the patients would like to be told.

The proposed draft of H3Africa Guidelines for informed consent for human Genomic Research is a step in the right direction.

CHAPTER 2.

INCIDENTAL FINDINGS: CONCEPTUAL CLARIFICATION AND DEBATE

In this chapter, we would put forward a working definition of incidental findings, as well as examine the current debate on the management of the same. Available definitions of incidental findings take their starting point from the definition provided by Susan Wolf and colleagues (2008b). In their 2008 article on "The Law of Incidental Findings in Human Subjects Research'(Wolf et al., 2008b), Susan Wolf and others defined incidental finding as a "finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study". In large scale genomic studies, it may be difficult to identify what is incidental or not, since anything may fall within the scope of study. Parens and colleagues (2013), for this reason, argue that the term 'incidental finding' is no longer pertinent. According to these scholars:

> As screening and interpreting data become simpler and as analysis pipelines are built to automate detection of known disease-associated mutations throughout a genome-the likelihood of uncovering many variants relevant to a large number of disorders will become the rule rather than the exception, and the term 'incidental finding' will not be pertinent (Parens et al., 2013).

In place of the term incidental findings, Parens and colleagues suggested 'individual genome result'. It suffice to argue here that there are large scale genomic projects in which incidental findings are possible and others in which they may not arise. Additionally, not all genomic researches are large scale genomic studies. Some genomic studies are designed to answer specific research questions. The emphasis here is on the researcher's intention. Some researchers engage in research with specific aim and objectives in mind. Anything which falls outside of this intention is an incidental finding.

Regardless the preceding point, fact remains that in research participants, incidental findings concerning individuals, do indeed arise in genomic research. As a result, genomic research has not gone past the age of incidental findings. Rather incidental findings in genomic research would only increase with the advancement of research technologies and approaches.

Some other scholars defined incidental findings differently. Green and colleagues (2013), defined incidental findings as "the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered"(Green et al., 2013). This definition appears to be consistent with United States Presidential Commission for the Study of Bioethical Issues twofold distinction between anticipatable and un-anticipatable incidental findings. An anticipatable incidental finding is a known logical consequence of a primary finding, while un-anticipatable incidental finding is simply not anticipated (United States, 2013).

Contrary to Green and colleagues, we argue that there is hardly anyway a finding can be incidental (from medieval Latin *incidentalis* meaning 'falling upon, unplanned') if it is a product of a deliberate search for it. We do, however, agree, as argued by Evans (2013), that an incidental finding may arise in the process of a systematic and methodic search for information relevant to research aim and objectives. Incidental findings are, nonetheless, unanticipated findings. Hence, Wolf and colleagues' definition of incidental findings comes close to the understanding of incidental finding as 'something unplanned'. Even when an incidental finding is discovered in the process of a systematic and methodic analysis, it is still outside of research aim and objectives. Consequently, we tentatively define incidental finding as an unanticipated finding discovered in the process of a systematic and methodic analysis of data for findings related to the research aim and objectives.

This point brings us to a final observation in this section; that is the distinction between incidental findings and primary findings. A primary finding, unlike incidental finding, is directly related to research aim or research objectives. Issues relating to management of incidental findings are proving difficult, particularly within the research setting, because of the perceived distinction between research and clinical care. We would address this difficulty in the next section.

2.1 Research Context versus Clinical Context

Research is commonly defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (Levine, 2003). Research is equally either therapeutic if it provides direct benefit for the research participants, or non-therapeutic if it does provide any direct healthcare benefits for the research participants. Generally, research aims at creating generalizable knowledge.

Research is to be distinguished from clinical care, which is oriented towards providing health benefits to the patients. For this reason, some scholars such as Solberg & Steinsbekk (2012) argue that researchers, unlike physicians, are not necessarily required to act for the health benefits of research participants. Unlike physicians who have a duty to follow up on a patient's health, there exists no relationship between researcher and research volunteers similar to doctor/patient relationship in the clinical context. This does not apply strictly to a researcher who equally has a physician/patient relationship with his research participants. In this situation, the researcher/physician has the duty to follow up on the participant's health. For the purpose of this study, our focus is on a researcher who has no physician-patient relationship with his participants.

Finally, research context may also be distinguished from clinical context in other ways. Tests, for example, which may be used to alter clinical care must be obtained in clinically approved laboratories. This is both an ethical and regulatory requirement for clinical use of any test. Research tests, on the other hand, do not have to meet such requirement. In other words, tests used within the context of clinical care must be obtained in clinically approved laboratories such as laboratories approved under the Clinical Laboratories Improvement Amendments (henceforth: CLIA) in United States (Clayton & Mcguire, 2012). Tests should not be used to alter clinical care if they are not validated by CLIA approved laboratories. On the contrary, in Nigeria there are no accredited laboratories (Amaefule, 2012) . However, since between 75% and 85 per cent indices for patient management come lab tests, the Federal ministry of Health insists that lab tests should only be used if they are obtained from a laboratory registered with Medical Laboratory Science Council of Nigeria (MLSCN). This move was necessitated by the need to reduce the existence of poor laboratories providing suboptimal services to patients. Accreditation is different from registration. Accreditation "is a process of validation established to ensure that medical laboratories deliver high quality services that meets the needs and requirements of their clients."(Health, 2012). Registration on the other hand, means that the laboratory has fulfilled certain basic requirements needed to function. The requirements include manpower, space, facility, equipment and minimal process documentation (Amaefule, 2012).

2.1.1 Participant and Contributor

We would refer, in this study, to participants and contributors simply as research participants. However, a little distinction needs to be made between a research contributor and

participant. A contributor is an "individual whose specimens or data are deposited in a repository or used in secondary research, while a participant is an individual about whom scientists obtain information through intervention or interaction, or about whom scientists obtain identifiable private information" (Ossorio, 2012).

2.1.2 Research Results and Incidental Findings

An incidental finding which arises within the context of research is a form of research result. In this essay, we shall define research result as "a finding discovered in the course of research". Some scientists, believe that research results are distinct from incidental findings (Wolf, 2008). We agree that these two terms should not be conflated. However, this distinction needs to be intelligently nuanced.

Every result or finding discovered during the course of research is a research result. Research result may be distinguished into different types: individual research result, aggregate research result and incidental findings. Beskow and colleagues, define aggregate result as "a summary or overall result arising from research" (Beskow et al., 2012). We define an individual research result, in this study, as a finding concerning an individual participant, discovered in the course of research and within the purview of the aim or objectives of the research. This last point distinguishes individual research result from incidental findings.

Some scientists hold that since incidental findings are unrelated to the scope of a study, researchers do not generally have an obligation to return such findings. Some other scholars argue that researchers do have an obligation to return incidental findings; still others make a distinction between secondary researchers and primary researchers. Richardson and Cho (Richardson & Cho, 2012) defined secondary researchers as those "who obtain access to the samples without entering into any direct relationship with those who contributed the samples, either by seeking the contributors' informed consent or otherwise". The term 'secondary research' does not imply that the research has no significance as other types of research. A primary researcher is one with direct, informed consent based relationship with participants.

2.2 Scope and Extent of Incidental Findings in Genomic Research

Incidental findings may arise in any of the four broad areas of genomic research. Misattributed paternity or misattributed lineage and unexpected discovery of genetic variant of

clinical significance, which is outside the scope of variant being studied, for examples, are not uncommon in genetic family studies. An extra-colonic finding in computed tomography colonography[1], and an unexpected mass or anatomical malformation, evidence of injury or infection may also be discovered in the process of structural magnetic resonance imaging of the brain. Incidental findings is not entirely new to medical or research practice. Its existence predates genomics. As far back as the early 1980s, doctors have had to deal with this phenomenon under the term incidentaloma. In medical practice of early 1980s, incidentaloma was conceived as a tumor "found by accident" during an examination or imaging for other reasons. Some others were also uncovered during autopsy and medical research (Kapoor et al., 2011). When the phenomenon first emerged, it was found to be a common problem of the adrenal gland, discovered during diagnostic imaging. These incidentalomas were often benign – though a very small percentage did turn out to be malignant -- and may not cause any clinically significant symptoms. When detected, managing these unapparent adrenal mass did not raise so much difficulty for the physician. The pressing challenge for the physician was to determine whether the lesion is active, and whether it is malignant or benign. The result of the test will influence his decision to treat the mass (Papierska et al., 2013, Geelhoed & Druy, 1982).

Over the decades, owing to advancement in technology, incidentalomas or incidental findings are now generated in large numbers. With the emergence of genomic research, managing these findings has also become trickier and more intense. Whole genome studies today, for example, can generate a large volume of health related information that may have clinical significance for the participants. Some of this would be directly related to the study aim and will be considered a 'pertinent finding'; some of this will be unexpected findings that are not directly related to the research question that the genomic researchers are trying to answer. And some of the researchers conducting this research, as demonstrated by Wolf and colleagues (2008a), may be inexperienced in handling these findings.

Incidental findings (Wolf, 2012) could arise at any point in the research process: from the baseline while recruiting subjects for research to analysis and dissemination of data. Wolf and colleagues (2012) offered two examples: a researcher may discover, during enrollment, that a potential research subject has elevated blood pressure. Secondly, a researcher who while using a

[1] This is a method of examining the inside of the colon by taking a series of x-rays.

genome-wide association study to investigate breast cancer, stumbles upon a mutation associated with colon cancer (Parens et al., 2013).

The prevalence of incidental findings in any genomic research may be influenced by type of genomic research, the research question, methodology of the research and the technologies employed. Incidental findings are equally not uncommon in genomic studies involving large number of subjects in population based investigation of relationships between genomic and phenotypic variations[2] (please confer Knoppers et al., 2013), or research involving collecting data on entire genome. Current and advanced technologies also have a potential for yielding high prevalence of incidental findings in research. Present studies conjecture an incidental finding of misattributed paternity at a prevalence of 10% for general population; an incidental finding between 13% to 84% (Milstein, 2008) of brain magnetic imaging scans and an incidental finding of extracolonic lesions in between 15% to 89% of participants (Wolf et al., 2008a, Morris et al., 2009, Krier & Green, 2013).

2.3 Incidental findings and the Inevitable Questions

Incidental findings is certainly challenging the research community to ask basic questions about the distinction between research and clinical care, the role of the researcher and diagnostic limit of research data. Scientists must equally consider the challenges of not reporting incidental findings to research participants and conversely: that is of reporting these findings with the potentials for psychological harm and trauma these findings may cause the participants or family members[3]. The web of difficulties, incidental finding is generating in genomic research, as Wolf and colleagues observed (Wolf, 2008), is "a ferocious tangle of science, medicine and ethics". This is capable of generating complex ethical, legal, professional and financial problems capable of undermining the importance of research in medicine. Couzin-Frankel (2011) is therefore, right to

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2 Population based studies include biobanks, longitudinal cohorts, social science, and genetic epidemiology research. Data collected from these studies often serve as a resource for future unspecified research. At the baseline assessement, findings may reveal serious life threatening conditions. Years after the assessement and storage of data, and with new technologies, researchers may also discover findings with important health implications for the contributor. The challenges often at this time have to do with reindentification and recontacting for the purpose of returning IFs.

3 Albeit we recognize that at the baseline, it is often difficult to determine whether risks involved in returning incidental findings to research subjects are more than minimal, establishing a Data Safety Monintoring Board (DSMB), may be one way of mitigating the potential for psychological harm. As a proposed point of departure, all genomic studies may be obliged to have a data satefy monitoring plan (DSMP). DSMP would essentially determine whether DSMB is required, and how findings are to be handled

describe the debate on incidental findings management, the 'most pressing issue in genetic studies'.

Incidental finding is raising important questions not only for researchers, but equally for Ethics Committees, funders, professional societies and human participants who generously volunteer to participate in research. Ness (2008), and Wolf and colleagues (2008a, 2008, 2012) identified some of these pressing questions. They include:

i. How do we protect the scientific enterprise while doing right to the human participants?

ii. Do researchers, including non-physician researchers, have an obligation to examine their data for incidental findings and recognize them?

iii. What should researchers do when they come across incidental findings?

iv. If the research testing is not done under clinically approved laboratories, how reliable is the test?

v. What, if anything, should the research participant be told or anticipate?

vi. Should the guardians of minor participants, legal proxies of adults or relatives of participants be informed of these findings?

Two voices could be contextualized in response to these questions: genomic libertarians and genomic skeptics[4]. (Allyse & Michie, 2013)

[4] This idea has been borrowed from clinical context. Two terms are commonly used to explain two positions on return of incidental findings: genetic libertarians and genetic empiricists. Genetic libertarians advocate for the full return of all genetic information, while genetic empiricists argue against sharing incidental findings since their clinical significance is largely unclear. In place of the term 'genetic empiricist', we have chosen to use genomic sceptics. The term genetic empiricist, we believe, fails to adequately explain counter position on return of incidental findings in genomic research. Genomic sceptics argue that even where there is clear clinical significance, researchers should not be obliged to return such findings. For the reason that, inter alia, it would encourage therapeutic misconception, and distract researchers from research aim and objectives.

2.3.1 Genomic Libertarians

Genomic libertarians argue that there is a general duty to return incidental findings. Research participants, they argue, have a right to know only if certain conditions are fulfilled. There are, however, disagreements over what type of incidental finding may be returned; who has the responsibility to return such incidental findings (care givers, primary researchers; and in case of repository research, bio-banks or the secondary researcher)?

Genomic libertarians propose five criteria (Zawati & Knoppers, 2012, Lockhart et al., 2012, United States, 2013), for the general duty to return incidental findings:

i. The findings are analytically valid.
ii. Returning them to the donor comports with applicable law.
iii. The donor has been offered that option of consenting to return of individual findings and has opted to receive them.
iv. The findings reveal an established and substantial risk of (A) a serious health condition, or (B) a serious condition of reproductive importance.
v. The findings are clinically actionable.

2.3.1.1 Analytic Validity

Bledsoe and colleagues (2012) define analytic validity as the "ability of a test to measure a particular characteristic accurately and reliably in a given specimen." Closely related to this is the test for clinical validity. Clinical validity may be defined as a "test's accuracy in detecting the presence of, or predicting the risk for a health condition or phenotype" (Ferreira-Gonzalez et al., 2008).

Within the context of research where the desire is to generate generalizable knowledge and not clinical care, the possibility of error is often high. In order to eliminate the possibility of false positive results and to address quality control concerns, the 2010 Guidelines on Human Biobanks and Genetic Research Databases mandated that "non-validated results from scientific research using human biological materials and data should not be reported back to the participants. This decision should be explained to them during the consent process" (Cooperation & Development, 2010).

Following this guideline, and similar guidelines, it is generally required that incidental findings undergo substantiation and validation in laboratories optimized for clinical care or

clinically approved laboratories, such as CLIA laboratories in the United States, before returning them to research participants.

2.3.1.2 Applicable Laws and the Phenomenon of Incidental Findings

Applicable laws relevant to how incidental findings may be managed stem from court proceedings, administrative and regulatory laws. The commonly cited case (Milstein, 2008, Wolf et al., 2008a, Wolf et al., 2008b), for supporting return of incidental findings is the *Grimes v. Kennedy Krieger Institute* case, where the highest court of Maryland asserted that a 'special relationship' exists between researchers and their research participants. This special relationship creates duties which require the investigator to completely and promptly inform the subjects of potential hazards existing from time to time because of the faith the research subject places in the researcher (Maryland Court Of, 2001).

Furthermore, certain international bodies, regional and national laws, guidelines and recommendations, favor return of incidental findings. In a recent document published by the United States Presidential Commission for the study of bioethical issues, researchers were encourage to anticipate and put in place necessary plans for communicating incidental findings (United States, 2013). The National Heart, Lung and Blood Institute of the National Institute of Health recommends that individual research results may be reported once certain conditions were met. Albeit there is often a tendency, as observed by Zawati and Knoppers (2012), to conflate individual research results with incidental findings in international documents, scientists who favor disclosure of genomic results, generally extend this recommendation to incidental findings. The conditions which must be satisfied include (Bookman et al., 2006):

a) There is a significant risk for disease
b) The disease should have serious health implications.
c) There is a proven therapeutic or preventative intervention available.
d) Only a test carried out in a clinically approved (CLIA) laboratories should be reported others should be labelled as 'research only'.

A similar position were earlier expressed by Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO) that "individual subjects…..be informed of any finding that relates to their health status" (Van Ness, 2008). The

Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Health et al., 2005) also states that "researchers have an obligation to disclose to the participant any material incidental findings, that is findings with significant welfare implications for the participant whether health-related or psychological, discovered in the course of research". Other national bodies such as American Society of Human Genetics and Canadian College of Medical Geneticists equally generally favor return of research results, albeit they differ on who may return these findings.

Albeit there are no legal laws relating to genomic research in Nigeria, National Regulatory Code for Human Subject Research (NREC), provides that research participants must be treated as partners in the research enterprise. As such, researchers must disclose any new finding that may significantly impact participants' health and well-being. The term 'new finding' in the Code may be broadly defined as including incidental findings. Such findings or what the Code calls are equally to be reported to institutional research Ethics Committees. A similar obligation is also imposed on researchers by the South African Government. Specifically, the 2003 South African Health Act (Schedule 3) obliges all researchers to disseminate research results, whether negative or positive, to research stakeholders in a timely and competent manner, including to participant communities as far as possible.

Recent recommendations from different national bodies such as American College of Medical Genetics and Genomics (ACMG), equally now require sequencing laboratories, though within clinical setting context, to 'actively' and 'systematically' search for 57 disease causing pathogenic mutations in genes where pathogenic variants can lead to disease with very high probability; and where early intervention is possible (Green et al., 2013). 25 of the 57 cause tumor/cancer related diseases, 23 lead to cardiovascular problems, mutations in seven genes cause Marfan and related syndromes, and two lone conditions (Ehlers-Danlos syndrome and malignant hyperthermia) (Green et al., 2013). The recommendation also says children should not be treated any differently from adults. The duty of informing the patients should be left to the ordering clinician. What this means, as explained by Evans (2013), is that 'a far reaching and complex informatics filters must now be applied to genetic data by the sequencing laboratory, in order to determine which of the many variants, present in the raw data predispose a patient to a preventable disease.

Notwithstanding the favorable disposition to return of incidental findings, there are certain national and international bodies which, however, discourage the return of research results in general and incidental findings in particular. Singapore Bioethics Advisory Committee, for example, proposes that:

> Donors should not expect any personal or direct benefit from the donation of tissue, including information of any medical condition or predisposition or likelihood of such discovered in the course of research on the sample. Likewise, researchers and tissue bankers should not be under an obligation to disclose such information to the donors, unless they have agreed to do so in advance of the donation (Committee, 2002).

The Advisory Committee believes that this is important in order to prevent therapeutic misconception, a situation whereby a contributor "inaccurately attributes therapeutic intent to research procedures" (Zawati & Knoppers, 2012). It remains unclear, however, if the committee's recommendation extends to primary researchers who have direct relationship with research participants.

2.3.1.3 Incidental Findings and the Consent of Participants

In addition to analytic validity and conformity to applicable laws, scholars also recommended that research participants must have expressly provided their consents to receiving such findings. Nigerian and international guidelines both recognize the importance of obtaining consent in research practice. Sections 37 and 38 of the 1999 Nigerian Constitution provides that every person shall be entitled to his privacy and freedom of thought. These sections form constitutional bases for a participant to indicate his or her preference for information. Any disclosure of information against the consent of the participant would be an invasion of his right to privacy. Privacy of individuals, Section F of the (Nigerian) National Regulatory Code for Human Subject (henceforth: NREC) research warns, may not be needlessly compromised. However, if lifesaving information are stumbled upon, and since researchers are also encouraged to treat research participants with respect, NREC also provides that a researcher may undertake a re-consent process to determine if the participants would like to receive any new finding.

It is not to be expected that, at least within Nigerian context, participants would be open to receive new information. This is because the genomic information may have serious implications for family relationships, personal and ethnic identity (Marshall et al., 2006). Africans generally

tend to be communalistic. Within such setting, community consultation would be key. As Jegede (2009a)observed already, "what exists in Africa, is communal or social autonomy as opposed to individual autonomy in the West". Communalism is the basis of existence in most African societies. The community is prior to the individual. The community's autonomy begins from where the individual's autonomy stops. An individual exists through others (Jegede, 2009a). Hence, African sense of the community would complicate the informed consent process. An African would probably not take part in research if his/her community does not permit. This point is also supported by Fagbemiro and Adebamowo (2014) point when they argued that participants, within African setting, would respond differently to genomics research because of embedded African cultural and religious beliefs. Societal norms, values and moral standards are quintessential in guiding the individuals in making decisions about participating in a research. 'Participation in research derives from communal values, common good, social goals, traditional practices, cooperative virtues and social relationship'.

The 1996 International Human genome Organization Statement (Knoppers, 2012, Organization, 1996) on the Principled Conduct of Genetic Research required that "choices to be informed or not with regard to results or incidental findings should be respected". The prevailing standard (Booth et al., 2010) in researcher/research subject relationship is that genetic results should never be forced on any individual.

Some other documents, however, advance a contrary argument. Recent recommendation from the American College of Medical Genetics and Genomics (ACMG) allows that individual autonomy, in a clinical care context, may be ignored for the patient's own good (Allyse & Michie, 2013, Rehm et al., 2013). This recommendation comes on the heels of some studies which revealed that research participants ordinarily expect that health anomalies be disclosed to them and discussed with a responsible physician regardless of whether they provided 'consent to receive them' (Booth et al., 2010). Notwithstanding, scholars who favor return of incidental findings do not generally take this as the standard. According to these scholars, the potentials for incidental findings, as well as how they would be handled, should be made known to research participants in the consent form. And the research participants' wishes 'not-to-receive' findings should always be honored.

2.3.1.4 Importance to Health and Reproductive Decision

The National Heart, Lung and Blood Institute also recommended that findings with important health implications for the research participants should be returned, if they revealed 'established' and 'substantial' associated risks (National Heart et al., 2010). In lieu of importance to health, Wolf and colleagues (2008a) use the term "strong net benefit" (Wolf et al., 2008a), that is, if the finding revealed a life threatening condition or an avoidable grave condition, then it should be returned.

Genomic libertarians, as observed by Clayton and McGuire (2012), generally 'favor returning of research results that could trigger life-saving interventions. There is however, less consensus, about whether research participants should be offered results with reproductive significance or personally meaningful'.

2.3.1.5 Clinically Actionable

A finding is said to be actionable if it has clinical utility, that is, if it could be used as a basis for an intervention directed towards improving someone's health status or preventing premature death or substantial morbidity. If such finding or information would significantly improve life quality or could avert serious adverse health conditions, it is also said to be actionable. Ferreira-Gonzalez and colleagues (2008), define clinical utility as "a balance between health-related benefits and the harms that can ensue from a genetic test". The balance must favor the likelihood that the finding would lead to improved health outcome. This would mean intervention is available, minimizing employment discrimination and long term psychological harm.

This final condition for reporting incidental findings is important. Since it shows, *inter alia,* that an incidental finding may not only be unrelated to the research aim and objectives, but also not clinically actionable. As a result, three forms of incidental finding should be distinguished here. An incidental finding may be:

a) Clinically actionable (the individual is at a high risk of future preventable or manageable health problem).

b) Not-clinically actionable (provides information for which there is no clinical action or has no implication for the individual's health status)

c) No-known clinical significance (implication for the individual's health is at the moment, unknown).

Following these three-fold distinction, we define incidental finding broadly, in this work as "**an unanticipated finding, with or without clinical significance, about a (research) subject, discovered in the process of a systematic and methodic analysis of data for findings related to the aim and objectives of (research) study**".

Incidental finding largely generates controversy, in genomic research, when it is an 'unanticipated clinically significant result'. In other words, it is a finding about a research subject who is at a high risk of future preventable or manageable health problem. No doubt there are other reasons, such as misattributed paternity, why incidental finding may generate controversy.

Owing to the sense of heritage, an incidental finding of misattributed paternity would treated differently within Nigerian setting. Because such finding may quickly lead to loss of identity, loss of rights to inherit, stigmatization and expulsion from the community. The individual would be labeled a bastard. Such remarks have been known to cause great psychological distress for individuals. Sequel to these reasons, Nigerians would generally not favor disclosure of incidental findings with misattributed paternity. And if they accidentally learn of this, such information would be guarded in secret, away from the ears of any third party.

But the frequencies of misattributed paternity in genomic research, are relatively low when compared to clinically actionable findings (Booth et al., 2012). When clinically actionable findings arise, how should they be handled? For genomic libertarians, insofar as the research subject has not opted out[5] from receiving such information, the finding has been validated and shown to be clinically actionable, there are ethical and legal duties to return such findings; to save life and

[5] Could someone stay neutral? Silence, for some libertarians, may be taken as consent however, when in doubt, when the research subject has not specifically indicated whether s/he would like receive or not receive and the researcher has discovered a clinically actionable finding, researchers should approach the subject to seek his/her consent again whether s/he would like to receive such findings.

Thus for libertarians

Opting out is a categorical NO to Ifs

Opting in is a categorical YES to Ifs

Neutral means that I should be asked again when you discover something that is of health importance for me. There are extreme libertarians who argue that clinically actionable findings should be returned to research subjects whether they opted to receive it or not.

prevent serious illness. The preceding statement equally answers the question of what kind of incidental finding may be returned: validated and clinically actionable findings.

Returning clinically significant information would demonstrate the researcher's concern for research subject's welfare and autonomy, and strengthens the fiduciary relationship between the researcher and the research subject. Genomic Libertarians describe these duties in different ways: duty of reciprocity and beneficence, a duty to rescue, respect for persons, and partial entrustment

2.3.1.6 Duty of Reciprocity and Beneficence

Duty of reciprocity is based on the following principle: if a research enterprise has benefited from the contributions of research participants, it is only appropriate that investigators and researchers benefit research participants in return by providing results of potential clinical value to the same (Beauchamp & Childress, 2001). From the Kantian perspective, this would ensure that participants are not used as mere means to an end. In addition, from the utilitarian perspective, it would also ensure that risks to participants are considerable reduced and benefits maximized.

'The duty to benefit research participants', as Wolf and colleagues (2008b) explained, "is a part of a broader duty of beneficence: to secure participants' well-being by maximizing benefits and minimizing harms". The researcher's duty to reciprocate kind gesture is a necessary consequence, flowing from the recognition of what research participants have contributed to the scientific enterprise. Illes and colleagues allude to this principle as the basis for grounding the duty to return clinically significant information to research participants (Illes et al., 2006).

Africans would probably be open to receiving lifesaving information. Welfare, Jegede asserts, is the central focus or reason why many Africans participate in research in the first place. Africans are interested in the social value of an activity taking place in their community (Jegede, 2009a). In an HIV/AIDS study which he conducted amongst the Yoruba people of Southwest Nigeria, Jegede observed that the Yoruba community wanted to know the *anfani*-meaning beneficence or benefit- of the study to their community(Jegede, 2009a). The *anfani* is collectively owned. When the individual gives his or her consent, what is projected is the interest of the community. Benefits and harm are judged or considered according to how they principally affect the community and secondarily the individual.

2.3.1.7 Respect for Persons

This ethical principle is based on the investigators/researchers' duty to respect the interests and autonomy of research participants. The principle of respect for persons implies research subject's rights to self-determination. According to Section of F of the (Nigerian) National Regulatory Code for Human Subjects Research, the principle of respect for persons requires researchers to treat participants as partners in research. As a result, research participants have a 'presumptive entitlement to information about themselves'. It would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information about themselves derived from their participation in research (Shalowitz & Miller, 2005). Letting research participants know, Knoppers and Chadwick argue (2005), while obtaining informed consent, that the researcher will be reciprocating their kind gesture by returning clinically significant findings is indeed a way for researchers to treat research participants respectfully.

Within African setting, this respect would also be extended to the community for reason of the unique relationship which exists between the individual and the community.

2.3.1.8 Duty to Rescue

The duty to rescue presupposes, *inter alia*, that when one is in a position to save life or help, and the risk to the rescuer is minimal or it involves slight sacrifice, then one has a moral duty to offer such help. The following words describe Thomas Scanlon's (1998) formulation of this principle: "If we can prevent something very bad from happening to someone by making a slight or even moderate sacrifice, it would be wrong not to do so".

i. The duty to rescue incorporates five features (Schöne-Seifert, 2009):
ii. The victims' visibility or identifiability;
iii. Acutely impending death of the victims;
iv. A reasonable chance of effective rescue;
v. Acceptable risks or costs to the rescuers;
vi. Exceptionality of occurrence.

These features are consistent with the second article of Quebec *Charter of Human Rights and Freedoms*(Due process -- right to medical access -- Supreme Court of Canada holds that ban on private health insurance violates Quebec charter of human rights and freedoms--Chaoulli v. Quebec (Attorney General), 2005 S.C.C. 35, 29272, [2005] S.C.J. No. 33 QUICKLAW (June 9, 2005), 2005) which states that "every human being whose life is in peril has a right to assistance...Every person must come to the aid of anyone whose life is in peril, either personally or calling for aid, by giving him the necessary and immediate physical assistance." Following this principle, genomic libertarians argue that if a researcher stumbles upon important life-saving data in his investigation, signifying that the research subject is at risk of death if s/he is not given clinical care, the researcher has a duty to immediately intimate such research subject.

Michael Ulrich (2013) cites this principle as a basis for returning incidental findings. According to him, 'utilizing the duty to rescue avoids conflating the return of genetic information with providing needed clinical care. Moreover, a rescue–based approach recognizes the ethical duties researchers have toward the research study and offers a mechanism for appropriately balancing these with obligations to individual subjects'. However, he observes, "the duty to rescue does not compel anyone to search out harm that they may be able to alleviate pain or save lives" (Ulrich, 2013).

This last point remains a contentious issue amongst genomic libertarians. Some would argue that the duty to rescue also obliges researchers to actively look for findings, as is the case with ACMG recommendations for clinical genome and exome sequencing, for which penetrance is high and clinical intervention is known.

2.3.1.9 Partial Entrustment Principle

Genomic libertarians are aware that applying the duties mentioned in the preceding paragraphs, to all researchers would be difficult, especially since there are a wide range of researcher/research subject relationships. Primary researchers maintain direct contact with their research participants, while such contact is absent in secondary researcher/contributor relationship. Thus, the duty to reciprocate; respect research participants or the duty to rescue may be impracticable in secondary researcher/contributor relationship. Consequently, some of them argued that the duty to return incidental findings should not be extended to secondary researchers. We would describe these ones moderate libertarians. Moreover, they added, secondary research

involves making use of banked samples, which are often anonymized thus making re-contacting the contributors impracticable.

In order to resolve this, Richardson and Cho (2012) proposed what they called partial entrustment model. This model was first developed by Belsky and Richardson (2004, 2004) to explain medical researchers' ancillary duty, albeit outside the purview of their study, to arrange for clinical care of at-risk research participants. The model argues that 'researchers have a duty to provide ancillary care to subjects of research, based on the principle that participation in research involves at least a partial, even if tacit, entrustment of health to the researchers' (Cho, 2008).

The aspects of research participants' health which are entrusted to the researchers' care, are those things that come to light through the study procedures, regardless their relatedness to research aim and objectives. Richardson and Cho explained further:

> Research participants entrust the relevant aspects of their health to researchers, not because they trust researchers; and not because they think they are entrusting them, rather, what is important is that research participants have waived their rights, even by way of blanket permission, that researchers should not probe their bodies or collect their medical histories (Richardson & Cho, 2012).

Following the waiver of research participants' rights, researchers retain the privilege to use freely the materials deposited to their care, as well as incur critical duties of safeguarding the values, such as privacy and confidentiality, which these rights normally protect. Hence, a researcher's ancillary care arises from the nature of informed consent process. Richardson and Cho concluded, 'it is in accepting the research participants' waiver that the researcher also take on ancillary-care obligations (Richardson & Cho, 2012).

This model, Richardson and Cho contend, applies well to secondary researchers, who must obtain permission from the sample collectors before making use of banked samples. By granting secondary researchers right to access banked samples, the sample collectors are also passing along the contributors' waivers of their privacy rights. By passing along the contributors' waivers of their privacy rights, they equally pass along the ancillary-care responsibilities which are attached to it (Richardson & Cho, 2012).

Genomic libertarians slightly defer on who may return incidental findings. A significant majority of genomic libertarians favor the notion that principal investigator or a senior member of the research team should return incidental finding. Some argue that biobanks have an important

role to play in managing incidental findings, while some favor genetic counselor, and others, the research subject's physician (Bemmels et al., 2012, Illes et al., 2008, Cho, 2008, Booth et al., 2010, Lockhart et al., 2012). Following the duties of reciprocity and beneficence; rescue; respect for persons; and partial entrustment, genomic libertarians maintained that researchers have an obligation to set up processes for identifying incidental findings, determining their clinical validity and utility, and returning these findings to research participants for evaluation and follow-up. The above duties, as Wolf and colleagues (2008b) explained, also incorporate the researcher's responsibilities of:

a) Developing a management plan for incidental findings in the research protocol
b) Discussing the possibility of incidental findings during the informed consent process and reveal how incidental findings will be managed
c) Addressing incidental findings in data
d) Verifying the presence of an incidental and assess whether the incidental has probable clinical or reproductive significance
e) Offering to disclose incidental findings of likely clinical or reproductive significance to the research participants

Finally, genomic research is such that they provide information that may be of clinical significance for family members of research participants. But genomic libertarians are divided over whether clinical significant information should be offered to family members of the research participants. Some are in agreement while others maintained that providing such information to third parties would be a breach of privacy and confidentiality of research participants. Others attempt to resolve this by saying, providing clinically significant information to family members of research participants can be carefully balanced against privacy and confidentiality of research participants through disclosure in the consent form, that such significant information would be disclosed to third parties.

2.3.2 Genomic Skeptics

Generally, genomic skeptics do not favor returning incidental findings. Returning incidental findings to research participants, they maintained, would encourage therapeutic

misconception; make the research enterprise financially burdensome; physically impracticable; harmful to research participants; and finally, may raise legal liabilities.

2.3.2.1 Therapeutic Misconception

Therapeutic misconception occurs when clinical care is conflated with research, or when there is a misunderstanding of the differences between research and clinical care. The principal aim of a researcher, Solberg and Steinsbekk (2012) argue, cannot be to act for the health benefit of the research participants. The desire to benefit, Clayton and McGuire (2012) add, is pleasant and should be encouraged however, researchers, unlike physicians, have clear responsibility of generating generalizable knowledge. In Ossorio's (2012) opinion, researchers duties to return incidental findings are constrained by the degree to which returning such findings would burden research aim and objectives. There is no duty to return (incidental) findings, if doing so would frustrate research aim.

Hence, clinical context must be carefully distinguished from research context. Researchers and research must equally be distinguished from physicians and clinics respectively. Research participants have no right to findings which were not generated within the context of clinical care. Clinical ethos, Solberg and Steinsbekk (2012) add, cannot be transferred to research setting. These two are different 'in an ethically relevant way'. Physicians have an obligation to act for the health benefit of their patients; however such obligation cannot be extended to a researcher who has no clinical relationship with the research subject. The obligation of researchers principally consists in maximizing the generation of knowledge. In the case of physician-researcher, depending on the nature of his relationship to the subject who may also be his patient, as well as the context of this relationship and the role the researcher-physician is performing, a physician-researcher may have clinical responsibilities to act for the health benefits of research participants/patients.

2.3.2.2 Financial Burden

Genomic skeptics also argue that if researchers are made to routinely return incidental findings, the cost of doing research would increase sharply. In order to minimize harm to research participants, before returning research results, many national and international guidelines often require that researchers validate and determine clinical significance of test results in laboratories optimized for clinical care, such as the Clinical Laboratory Improvement Amendments approved

laboratories in the United States (Bledsoe et al., 2012). The cost of determining the clinical significance and validity of such tests are high. Presently, many research investigations are carried out in laboratories not optimized for clinical care. Creating an obligation for researchers to return findings and extending the same to secondary researchers who make use of repositories such as bio-banks, would make the already expensive research enterprise, more financially burdensome. The negative impact on the research enterprise would be enormous, since it would create a disincentive for creating repositories, and by extension, for conducting research.

This assertion has been confirmed by Solomon and colleagues (2012) in a study on 'Incidental Medical Information in Whole-Exome Sequencing', where they discovered that a large amount of effort (financial and personnel) was required to return only one incidental genome variant found through whole-exome sequencing. With the current advanced technology employed in genomic research, creating an obligation to return findings would distract researchers from fulfilling research aim and objectives. Bledsoe and colleagues do agree that certain analytically and clinically validated results with important health implications may be returned to research participants. However, routine evaluation and return of incidental findings by all secondary researchers and repositories, are unjustifiable (Bledsoe et al., 2013).

In addition to financial burden, disclosure policy, Solberg and Steinsbekk (2012) conjecture, would give rise to increased medicalization of individuals and unnecessary use of healthcare system. According to Solberg and Steinsbekk (2012):

> Presumably healthy persons might become preoccupied with genetics, with the 'secrets' that they think are hidden in the sequence…..with individual prevention possibilities. They would probably demand follow-up programs to handle their risks for future diseases, testing of family members, increased prenatal diagnostic and so on…The irony then is that the same researchers and research institution that wanted to combat the increasing medicalization of individuals….by their public health research, risk ending up with a more thorough medicalization of the local community than they ever imagined. This might be the consequence, not because the researchers support such a development, but because 'good ethics' demands it…(this) might reduce the intrinsic value of research when individuals that solely would like to contribute to the greater good no longer have this opportunity.

2.3.2.3 Harm to Research participants

Clayton and McGuire (2012) argue that creating an obligation to routinely return incidental findings radically underestimates the difficulty of helping people to understand complex and

probabilistic genomic information; and sometimes, the researchers' lack of expertise to interpret the clinical significance. In addition, creating an obligation to return incidental findings equally ignores the reality of false-positive incidental findings which are capable of providing misleading or incorrect diagnostic or prognostic information (Kohane et al., 2012). There are also dangers that such information may be misinterpreted or inappropriately followed-up (Clayton & Mcguire, 2012). Additionally, research participants may be given information for which they are not prepared; or exposed to unnecessary treatment. All of which can subject research volunteers to significant physical and psychological harm. However, no harm would be caused if no obligation to routinely return incidental findings is created.

2.3.2.4 Feasibility and Practicability

In a research where researcher maintains direct contact with the research participants, returning validated findings may be practicable. But this cannot be said of studies carried out with deposited samples. These samples are often anonymized, thus making re-identification challenging. Even where re-identification is possible, there would still be the challenge of re-contacting research participants to offer them clinically significant findings. Samples may have been collected years back and research participants may have changed location or moved somewhere, thus making re-contacting impracticable. And where re-identification and re-contacting are possible, because the repositories retained link to research subject's contact details, skeptics argue, re-contacting should not be encouraged. Re-identifying research participants for the purpose of re-contacting them to offer them findings, Bledsoe and colleagues (2012) observe, puts research participants at risks of losing their privacy, and confidentiality of data.

Samples may also be lost in the process of transition. To protect the confidentiality of research participants' data, samples are often re-coded before handing them over to researchers. Researchers also must hand over these samples to others for analysis in the research laboratory. As more people become involved, it is statistically more probable, according to Bledsoe and colleagues (2012), that errors would occur and samples get mixed-up. There may be grave implications if such results were returned to research participants.

2.3.2.5 Legal Liability

Genomic skeptics also argue that creating an obligation to disclose incidental findings would have unintended consequences for individual researchers (Clayton & Mcguire, 2012). Presently, Clayton and McGuire observe, there are no legislations requiring disclosure of research results, and no lawsuits have found researchers liable for failing to return incidental findings. There are equally no clear indications on when and whether a researcher should be held liable for failing to return incidental findings to research participants (Pike et al., 2013).

However, as international and national guidelines continue to suggest that there is an ethical obligation to return findings, and as these guidelines become a routine practice, researchers may now be legally required to make return of findings in general, and incidental findings in particular, a standard of care practice. This is the way tort law functions (Clayton & Mcguire, 2012, Pike et al., 2013). The negative impact on the research enterprise would be great, since it would expose the researcher to legal liability for negligence if results are not returned.

Following these reasons of financial burden, and the risks of harm to research participants, legal liabilities, practical implementation issues, and therapeutic misconception, genomic skeptics argue that creating an obligation for researchers to routinely return incidental findings to individual research participants would negatively affect the development research enterprise, discourage researchers and sponsors. In lieu of framing the question around returning findings to benefit individual interests, some others argue that a summary result may be presented to the general public (Beskow et al., 2012). A summary result, Beskow and colleagues (2012) maintained, though not a substitute for meeting the obligations of individual results (incidental findings) may serve as a powerful and effective means of demonstrating respect for research participants, gratitude for their contributions to research, and updating research participants on the progress of the research. This is, however, still a suggestion. An empirical study would be needed to determine research participants' preferences on disclosure of incidental findings, as well as current practices. This would be the primary focus of the second chapter, where we would attempt a systematic review of empirical studies on institutions' and research participants' preferences on the management of incidental findings.

CHAPTER 3.

SYSTEMATIC REVIEW OF ATTITUDES, PRACTICES AND PERSPECTIVES ON INCIDENTAL FINDINGS MANAGEMENT

In this chapter, we would systematically review various empirical studies on incidental findings management. This would be achieved in different sections. In the first section, we would describe the method and materials. An explanation of data extraction process would follow after which we shall present our results.

3.1 Method and Materials

A literature search was carried out between the 20th and 23rd of October, 2013, using PubMed search engine **http://www.ncbi.nlm.nih.gov/pubmed/** and in Genetics in Medicine website **http://www.nature.com/gim/journal/vaop/ncurrent/index.html** (official journal of the American College of Medical Genetics and Genomics), to identify potentially relevant English publications. A combination of unique phrases- 'incidental findings', incidental findings genomic research', 'return incidental findings', 'return genomic results', 'managing incidental findings', 'reporting incidental findings'- were entered in both websites. The articles were not restricted to any particular years. Certain filters such as open and free, were also selected in Genetics in Medicine website. Article types were researches, and they were sorted by relevance to the unique phrases entered into the search engine. Only 'empirical studies', which examined how scientists and other stakeholders would handle incidental findings, or in any way explored how scientists and stakeholders would manage incidental findings in any of the four broad areas of genomic research were selected from both websites. Other studies such as opinions and commentaries were excluded. This study was approved by the Ethical Committee of the University of Ilorin Teaching Hospital.

3.2 Data Extraction Process

Using the filters identified and the criteria mentioned above, 8 articles were selected from official journal of the American College of Medical Genetics and Genomics and 13 articles were

selected, using PubMed search engine. They were all carefully entered into EndNote database (version X6; Thomson Reuters). 1 duplicate reference (Green et al., 2012b) was removed, 1 study (Wolf et al., 2008a) was dropped by two reviewers (reason-not an empirical study), who were asked to review the identified articles[6], thus leaving us with 19 articles, published in English language, which were systematically reviewed (Downing et al., 2013, Dressler et al., 2012, Driessnack et al., 2013, Fernandez et al., 2013, Ferriere & Van Ness, 2012, Goddard et al., 2013, Green et al., 2012b, Green et al., 2012a, Haga et al., 2011, Haga et al., 2012a, Haga et al., 2012b, Johnson et al., 2012/04, Klitzman et al., 2013, Lawrenz & Sobotka, 2008, Lohn et al., 2013, Master et al., 2013, Shahmirzadi et al., 2013, Simon et al., 2011, Williams et al., 2012, Wolf et al., 2012).

Data such as author(s), title, country of origin, study aims, participant description, year of publication, attitudes toward incidental findings, perspectives, reasons for attitudes/perspectives, field of genomic research, etc., were extracted and entered into STATA (version 12) for detailed description. Find the general characteristics of the articles in table 3.1 below:

General Characteristics

	Author_ID	Year	Sample Size	Country
1	Ferriere and Ness	2012	10	United States of America
2	Green et al	2012	16	United States of America
3	Dressler et al	2012	31	United States of America
4	Simon et al	2011	34	United States of America
5	Haga et al	2012	45	United States of America
6	Haga et al	2012	21	United states of America
7	Downing et al	2013	50	United States of America
8	Williams et al	2012	53	United States of America
9	Fernandez et al	2013	74	Canada
10	Master et al		100	Canada

[6] A moral philosopher and a statistician were asked to review the 20 studies. The studies were reviewed based on whether they were empirical studies or not. The two reviewers were unanimous in accepting 19 studies for review and dropping 1, for not being an empirical study.

11	Driessnack et al	2013	166	United States of America
12	Shahmirzahi et al		200	United States of America
13	Lohn et al	2013	210	Canada
14	Klitzman et al	2013	254	United States of America
15	Lawrenz and Sobotka	2008	1023	United States of America
16	Haga et al	2012	1139	United States of America
17	Susan et al	2012	2395	United States of America
18	Johnson et al	2012	2395	United States of America
19	Goddard et al	2013		United States of America

Table 3.1- Table shows the general characteristics of reviewed studies. The characteristics include author identification, year of publication of study, sample size and country where study was conducted.

The reviewed studies varied from studies involving human subjects (n=15) to studies involving documents and guidelines (n=4) for managing incidental findings. Majority (n=12) of the studies were carried out within non-clinical setting, that is, in a setting where there exists no physician/patient relationship between the researcher and the research participants.

To ensure standardization and aid pattern recognition, a data extraction form (See Appendix 1) was developed. The form was piloted with three random studies. Changes were made to the form as a result of the pilot test[7].

All authors with known email addresses (18 authors) were re-contacted for a second review of the extracted data from their studies. Seven authors responded (response rate at 38.9%). Minor changes, relating to source of funding, population description etc., were made as a result of the second review. This study reviewed all 19 studies. The studies were conducted largely in the

[7] The pilot test shows that certain questions, such as the duration of the duty to return, were considered by a few studies and not captured in the data extraction form. As a result, changes were made to the data extraction form reflect these important questions.

United States of America (n=16) and Canada (n=3). The 19 studies examined views of IRB chairs, researchers, geneticists and genetic personnel, public and patients towards incidental findings

3.3 Result

The result of the systematic review would be presented under the following headings:

A. Understanding of incidental findings in Genomic Research
B. Incidental findings management preference
C. Conditions for returning incidental findings
D. Factors affecting return of Incidental findings
E. Who should return incidental findings
F. To whom

3.3.1 Description of Incidental Findings

Our review of existing studies reveals four descriptions of incidental findings. Studies asked their participants how they would describe incidental findings and a significant majority in each study tended to describe incidental findings under the following headings: 'unexpected results', 'a finding unrelated to study aims', 'findings beyond study aims' and 'extra or unsolicited information' (Table 3.2). Three studies, however, did not provide any information about how their participants perceived incidental findings.

Incidental Findings Description

Definition of Incidental Findings	Freq.	Percent

Unexpected finding	3	15.79
Unrelated to study aims	8	42.11
Finding beyond study aim	3	15.79
Extra information	2	10.53
Provided no resp.	3	15.79
Total	19	100.00

Table 3.2: Table shows the various understanding of incidental findings. Many defined incidental finding as a finding unrelated to study aims.

3.3.2 Incidental Finding Management Preference

Majority of participants in 17 studies want results of incidental findings returned to them regardless of whether research took place in clinical (where there exists a physician/patient relationship between the researcher and research participants) or non-clinical context (Table 3.3). Geneticists, researchers, IRB chairs and professionals, as well as study participants demonstrated favorable disposition towards the return of incidental findings. The general support for the return of incidental findings, both within clinical and non-clinical contexts were also evident in the key conclusions of authors from the reviewed studies.

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Context of Study

Return Incidental Findings	**Non-clinical**	**Clinical**	**Total**
Majority Yes	10	7	17
	83.33	100.00	89.47
Minority Yes	1	0	1
	8.33	0.00	5.26
Fairly balanced	1	0	1

	8.33	0.00	5.26
Total	12	7	19
	100.00	100.00	100.00

Fisher's exact = 1.00

Table 3.3 Table showing statistical relationship between returning Incidental Findings and context of study

Analysis of these studies shows that there is no statistical relationship between the openness to return incidental findings and context of study (Fisher's exact = 1.00).

3.3.3 Type and Conditions for Returning Incidental Findings

The review of existing studies equally shows the various types of incidental findings, which may be returned in genomic research, as well as the conditions for returning the same. Some of the types and conditions include analytically valid findings; findings with serious health condition; clinically actionable and significant findings; serious but untreatable findings; non-genetic findings; and non-genetic findings measured at enrollment. Some studies mentioned that researchers may return incidental findings only if returning conforms to applicable laws and the subject has not opted out of receiving. The result of our study equally indicated that 13 studies (68.42%) concluded that a majority of their research participants want clinically actionable findings returned, and findings with serious health conditions discovered within clinical setting, returned. There is statistical relationship between context of study and whether findings with serious health conditions should be returned (fisher's exact 0.217). Only a few studies examined the duration of the obligation to return incidental findings. Responses for duration of the obligation to return range from research period to indefinitely (see table 3.4)

Duration of Obligation to Return

	Majority Yes	Minority Yes	Fairly balanced	Provided no data/Said No/Unclear data

Length of disclosure should extends only to project period	5.26%	0.0%	0.0%	94.74%
Length of disclosure extends to continued access to data	0.0%	5.26%	0.0%	94.74%
Length of disclosure extends indefinitely	0.0%	5.26%	5.26%	89.47%

Table 3.4- Table shows duration of obligation to return incidental findings discovered during research.

The statistical output presented in the table above shows that the question of period of the duty to return incidental findings has not been sufficiently explored.

3.3.4 Factors and Impacts of Returning of Incidental Findings

Some literatures indicated in their empirical studies that very few believe that the difference between research and clinical care, unwillingness of researchers to promote therapeutic misconception, resource and financial implication of returning findings, psychological harm and potential legal liabilities, would influence the decision to return incidental findings. Few also believe that return of incidental findings shows respect to study participants, would encourage participation in research and would help participants to take preventive measure.

Factors and Impacts of Returning of Incidental Finding

	Majority Yes	Minority Yes	Fairly balanced	Provided no data/Said No/Unclear data
Research is not clinical care	5.26%	0.0%	10.53%	84.21%
Research is not conducted in labs optimized for clinical care	0.0%	0.0%	10.53%	89.47%
Returning raises privacy and confidentialities issues	5.26%	5.26%	10.53%	78.95%
Returning may lead to discrimination	5.26%	5.26%	10.53%	78.95%
Returning has potential legal liabilities	0.0%	10.53%	0.0%	89.47%
Psychological Harm	15.79%	0.0%	15.79%	68.42%
Resource intensive and financially burdensome	21.05%	0.0%	5.26%	73.68%

Table 3.5 – Table showing the different factors which may influence the decision to return incidental findings.

This Statistical output shows that the question of the factors which may influence incidental findings has also not been sufficiently explored. From the studies which explored the question on psychological harm, context of study was also found to have a statistical relationship with whether harm would occur if incidental findings are returned (Fisher's exact = 0.31).

3.3.5 Recipient of Incidental Findings

The result of our systematic review also shows that the response to this question varied. A significant number of the reviewed studies (52.63%) concluded that a majority of the research participants favors returning incidental findings to research participants or patients. Other opinions were expressed. A few indicated that family members should be informed if condition is inheritable (5.26%) and guardians should be informed if the subject is a child (5.26%).

3.3.6 Who Should Return Findings?

This question has not been satisfactorily studied. A few suggestions were proposed. Some of them include researchers or appropriately trained personnel. A number of empirical studies (15.79%) concluded that their research participants want incidental findings returned by subject's physician**.**

3.3.7 Suggestions for Improving the Management of Incidental Findings

A few suggestions for improving incidental findings management were offered by a significant minority. Some of the suggestions include the need to anticipate incidental findings before study and offering genetic counseling before returning incidental findings.

Studies conducted within research setting indicated a fair tension amongst researchers on whether incidental findings should be managed on an individual basis or there should be a general policy for managing incidental findings. One study revealed that some participants would want serious and preventable incidental findings returned regardless of the patient's or subject's preference to receive the same.

Suggestions for Improving Incidental Findings (IFs) Management

	Majority Yes	Minority Yes	Fairly balanced	Provided no data/Said No/Unclear data

Researchers should anticipate incidental findings in genomic studies	26.32%	0.0%	5.26%	68.42%
Override subject wishes if condition is preventable and actionable	0.0%	15.79%	0.0%	84.21%
There should be a general policy for managing IFs	5.26%	10.53%	10.53%	73.68%
Genetic counselling should be offered before returning Ifs	21.1%	10.5%	0.0%	68.4%
Incidental findings should be managed on individual cases alone	15.79%	0.0%	10.53%	73.68%
Researchers have a duty to look for IFs	10.53%	0.0%	5.26%	84.21%

Table 3.6 – Table showing different suggestions for managing incidental findings discovered in research. Table also shows that this question needs to be further explored.

3.3.8 Limitation and Relevance of Study

This study has limitations. We are aware that the filters we selected, as well as the strict criteria used for excluding and including studies for the systematic review, may have ruled out potential studies which could have been included in this review, especially studies which are neither open nor free.

Secondly, we observed that some studies had missing information on participant characteristics, which made it difficult to compare information across studies or identify whether certain characteristics such as religious views, marital status or occupation may have been responsible for the attitudes or reasons given for disclosing incidental findings. Finally, this review has pooled resources, not only from studies which assessed views or perspectives of individual human beings on ancillary findings, but empirical studies on policies and regulations on incidental findings. This has also affected how the data are organized and analyzed.

CHAPTER 4.

HERMENEUTIC DISCUSSION

The systematic review of existing studies on incidental findings management shows that majority of their study participants want incidental findings especially clinical actionable findings or findings which indicate serious health conditions returned. However, this finding largely reflects the views of Northern American because there was little published data on African, European, New Zealand, Australian and Asian perspectives on the management of incidental findings in genomic research. The continued absence of these continents' voices in this discourse questions the consensus to return incidental findings to research participants. Given the impact of religion, culture, literacy, gender attitudes and inter-gender relationships, marital status etc., on worldviews and attitudes to research ethics in different parts of the world, it is imperative that studies should be carried out in these continents in order to gain their opinions on return of incidental findings in genomic research rather than impose expectations based on findings from other environment. Africans, for example, have been described by Mbiti (1969) as notoriously religious. This point has been confirmed in more recent studies (Jegede, 2009b). They take their religion everywhere they go, to their offices, shops, kitchen, markets etc. Wherever an African man goes, there is his religion. African man and his religion are so tightly connected that without the one, the other cannot exist. As a result, it would be important to study how religion, and culture, would affect attitudes and dispositions to incidental findings in genomic research.

In the hermeneutic phenomenological discussion which follows, we shall be applying hermeneutics as conceived by Heidegger in our analysis. For Heidegger, hermeneutics is hermeneutic phenomenology. In the subsequent sections, I will define phenomenology, hermeneutic phenomenology, and how the latter can help to provide some answers to the questions raised by ethical issues pertaining to return of incidental findings in genomic research.

4.1 Defining Phenomenology

Phenomenology is a radical way of doing philosophy. It is a practice. According to Moran (2002):

> Phenomenology is best understood as a radical, anti-traditional style of philosophizing, which emphasizes the attempt to get to the truth of matters, to describe *phenomena*, in the broadest sense as whatever appears in the manner in which it appears, that is, as it manifests itself to consciousness of the experiencer."

The first step in phenomenological examination is the attempt to delimit all presuppositions, assumptions and prejudices such as cultural, scientific, religious or everyday experiences. All a priori knowledge has the potential of compromising our perception of reality. For the phenomenologist, a phenomenological reductionism is indispensable for a good research. A priori knowledge would blind the researcher to the reality of what is being observed. For this reason, Frankl (1988) defined phenomenology as "an attempt to describe the way in which man understands himself, in which he interprets his own existence, far from preconceived patterns of interpretation and explanation such as are furnished by psychodynamic or socio-economic hypotheses." This is Neo-Cartesianism.[8] Phenomenologists are optimistic that the phenomenological attitude would get the researcher to the true essences of things, since phenomenology emphasizes the need to describe things as they appear to consciousness, free from all presuppositions.

Edmund Husserl is often referred to as the father of transcendental phenomenology[9]. From the very beginning of his philosophical speculation; Husserl had emphasized the need for the researcher to begin from an assumption-less point, that is, the need to discard theorizing in favour of description of what is given in intuition. He must not take anything for granted but must become aware of his preconceptions and set them aside. The researcher must not allow his personal worldview or his presuppositions to get in the way of pure consideration of the subject matter as it is given to us. The researcher must become unbiased; he must let what is, show itself. This is the clarion call of phenomenology, which is an invitation to return 'back to the things themselves'(Moran, 2002). And it was first announced in Husserl's work *Logical Investigations.*

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[8] From Descartes. He proposed a methodic doubting of all existing realities. Only such way of viewing the world can get us to the essences of things.

[9] It is a three step approach to study of reality. It involves looking at the phenomena, being conscious of the phenomena, intentionality and bracketing (ie separating the phenoma from one's own beliefs and experiences)

4.1.1 *Eidetic* Phenomenological Reductionism

In his work *Logical Investigation*, Husserl set out to give philosophy an unshakeable foundation, and establish it as a strict science (*strenge wissenshaft)* by means of a more radically conceived Cartesian procedure(Husserl, 1983, Laverty, 2003). He believed that reality has a core essence which can be intuited by identifying preconceptions and setting them aside. This act of putting aside is referred to as "*eidetic* phenomenological reduction" (Kafle, 2011). *En fait*[10], Husserl argues, reduction is key to a good phenomenological attitude. It is a transition from a simplistic to a more reflective approach of reality. This is suspending (*epoche*) judgment or effectively erasing the world of speculation by returning the phenomena to its primordial state (Husserl, 1962, Kakkori, 2009). This act means systematic removal of accidental aspects. Phenomenological reductionism is essential in order to prevent researchers from being implicated in the researched; since it gives them new eyes freshly as for the first time, and virgin consciousness. It is equally important for ridding ourselves of all biases, secure the purity of the observer's detachment, so that s/he can encounter things as they are in themselves, free from bias (Moerer-Urdahl & Creswell, 2004). As Husserl (1970) himself asserts, phenomenological reductionism or the act of setting aside "creates a unique sort of philosophical solitude, which is the fundamental methodical requirement for a truly radical philosophy...it is I who practice the *epoche*, I who interrogate, as phenomenon, the world which is now valid for me according to its being and being-such." Thus, the goal of phenomenology, for Husserl, is a descriptive, detached analysis of consciousness in which objects, as their correlates, are constituted (Husserl, 1962). All philosophical problems, all failed empirical studies, according to Husserl, are a result of improper interpretation of experience, coloured by presuppositions. Hence, to avoid this impasse, he advocated a phenomenological attitude, which consists of describing *phenomena* of consciousness as accurately as possible (Mehta, 1976).

Husserl's transcendental phenomenology has criticized by many. Dennett for example, argues that traditional phenomenology is not any different from Introspectionist psychology and Impressionist movement; in addition one may add Cartesianism, which asks us to take introspective look into ourselves with aim of setting aside our presuppositions. But introspection, he adds, produces very little that can be objectively verified, which is unscientific. This, he says

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[10] In fact

would give many an opportunity to create false things and personal assumptions that do not exist. Traditional phenomenology must become scientific and make it possible for others verify the truism in our assertions. In place of traditional phenomenology which has empowered many to be judges in their own case, Dennett suggested heterophenomenology. Heterophenomenology makes it easy for others to judge our assertions with neutrality and objectivity of physical sciences, because it focuses on the actual going-ons in the brain and sub personal mechanisms which are not introspectively available (Dennett, 1991, Dennett, 2007). Some other scholars suggested neurophenomenology. Put simply, in neurophenomenology, evidences produced by one person are compared with the lived experiences of others.

Husserl's traditional phenomenology would also find little support within African setting. For reasons that, community, social norms, religion, as well as culture, play important roles in African man's disposition to life. As a result it would be difficult to ask an African isolate or set aside his religion, community or culture. In fact, for Mbiti (1969), life in Africa is anchored on religion, on culture, community life etc. This point has already been confirmed in the 2004 survey carried out by British Broadcasting Cooperation which described Nigeria, for example, as one of the most religious countries in the world. Thus it would be suicidal for an African to set aside these realities.

4.1.2 Transitioning to Hermeneutic Phenomenology

The core of Husserl's pure phenomenology, Crotty (1996) argues, is the attempt to separate one's subjective experience or the noetic from the objective phenomena or the neomatic via *epoche*. Phenomenology asks us to be open to new perspectives and insights. Important differences also exist between pure (transcendental) phenomenology and hermeneutic phenomenology[11]. Pure phenomenology, as explained by Husserl, has a core essence which can be intuited and studied objectively through phenomenological reduction (*epoche*). On the other hand, hermeneutic phenomenology attempts to go beyond description in order to discover how preconceptions and historicalities may influence[12] our decisions or perceptions. In other words, with transcendental

[11] Hermeneutic phenomenology, neurophenomenology, heterophenomenology are different attempts of correcting pure transcendental phenomenology of Husserl. They equally represent the different forms of phenomenology after Husserl.

[12] Hermeneutic phenomenology is particularly interested in underlying influences of our perceptions and decisions. Hermeneutic phenomenolgy asks the question, "what may influence us?" or 'what has influenced us?"

phenomenology, researchers are interested in describing what is given to them, and restricting themselves from making assertions which are supported by appropriate intuitive validations; while hermeneutic phenomenology insists that researchers must make sense of what is given to them through interpretation (Finlay, 2012). For this reason, hermeneutic phenomenology, Kafle (2011) says, "is focused on subjective experiences of individuals and groups. It is an attempt to unveil the world as experienced by the subject through their life world stories." More importantly, hermeneutic phenomenology is a willingness to "undergo a process so that what is, may emerge and show itself" (Wilcke, 2002).

The transition from pure transcendental phenomenology to hermeneutic phenomenology was initiated by Heidegger[13], who did not reject phenomenology in its entirety. However, he was skeptical that a pure phenomenological attitude would set philosophy on the right foundation. For him, this solid foundation would only be achieved when phenomenology becomes interpretive, that is, when it becomes hermeneutical. Literally, hermeneutics is derived from the Greek *hermeneia.* Sandra M Schneiders and Raymond Brown provide a range of possible interpretations of this Greek word. First, *hermeneia* could refer to interpretation by *speech* itself, 'inasmuch as language brings to expression and interprets what is in one's mind'. Secondly, it could refer to the process of translation from one language to another, or an interpretation by commentary and explanation (Brown & Schneiders, 1990). Initially, hermeneutics was applied to the interpretation of biblical texts. But with the contributions of such philosophers as Heidegger, it came to be known as "the theory and practice of interpretation and understanding in different kinds of human contexts" (Odman, 1988, Wilcke, 2002).

For Heidegger (2008), all description is always already an interpretation. According to him:

> When an assertion is made, some fore-conception is always implied; but it remains for the most part inconspicuous, because language already hides in itself a developed way of conceiving (Heidegger, 2008).

For Heidegger, an individual is born in the world and responds to it by thinking, interpreting and understanding'. In *Being and Time,* he tells us that "thinking is our own interpretation of coming to understand in a new way. To be human is to interpret" (Heidegger,

[13] In addition to the above, in Husserl's pure phenomenology, there is a call to jettison or bracket all presuppositions. in Heidegger's hermeneutic phenomenology, this call is thrown out. Heidegger believes that such call was unncessary, and, in fact, destructive to the new ontology (ie the study of being).

2008). According to him, the factual existing human being is the basic fact and the source of all projects of understanding. But human beings are never "just there", *vorhanden*, but rather they have a priori structure as existents. Human consciousness, he explains, is never separate from the world. *En fait,* it is a formation of historically lived experience. Human beings are not cut off from the world. Human beings think and interpret because, as *Daseins*[14], they are beings-in-the-world.

4.1.3 The Researcher as a Being-in-the World

Being-in-the-world, for Heidegger, is the most basic and constitutive state of *Dasein.* This view of humans as being-in-the-world is Heidegger's own aversion for the Cartesian solipsistic thinking ego. In other words, it is Heidegger's rejection of Cartesian methodic doubt. Being-in-the-world means that man dwells upon the world. He is thrown and concretely immersed in the concrete world of concrete individuals. Being-in means man can never be conceived in isolation. This point is especially true of African culture, where the individual is never separated from his community. Put differently, communalism is the basis of life in Africa. Human person dwells alongside others in the world. The world here, means a context, an environment, a set of references and assignments within which any meaning is located (Moran, 2002). There is no isolated being; no *Dasein* without other existents. An African man especially cannot be conceived in isolation of socio-cultural context. He is always a being-with-others, or what Heidegger called *mit-sein.* The existence of others is not merely accidental but a necessity of thought which is constitutive of everyone's being (Blackham, 1974).

Furthermore, there are a number of things which shape an African as being-in-the-world. Many of them are hidden and thus, require interpretation in order for their existence to be understood. But every encounter involves an interpretation influenced by an individual's background or historicality. Human historicality is what culture, religion or science gives the individual from birth and is handed down, presenting ways of understanding the world. *En fait,* Heidegger says understanding is *Dasein's* own ability to stand his own thrownness. Understanding

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[14] Dasein is a German word for "being there" or "presence" ("da" which means "there" and "sein" which means "being". Philosophy, Heidegger believes, should be able to tell us what being is and where. Heidegger uses the word dasein to show that a good account of being must of necessity include the fact that being is 'there"; 'there' is the world. Being is constantly embedded and immersed in the tangible, physical day to day world. In summary, dasein is an inherently social being who already operates with a pre-theoretical grasp of the a priori structures that make possible particular modes of Being (confer Stanford encyclopedia). No one expresses this Being better than human beings. Human beings are called daseins because they exist in the world and inhabit it.

does not tell us how we think, but how we are and what influences us. It is through this understanding that one determines what is 'real' or not (Laverty, 2003). In other words, all understanding is connected to a given set of fore-structures, including one's historicality, which cannot be eliminated. Presupposition is a basic structure of being in the world. This is not something one can put side or bracket. On the contrary, one needs to become as aware as possible and account for these interpretive influences. "Meaning is found as we are constructed by the world while at the same time we are constructing this world from our own background and experiences" (Laverty, 2003).

Heidegger's hermeneutic phenomenology would be easily embraced by nearly all Africans because of the unique and complex relationship between sociocultural beliefs and outlook to life. An African is one who finds himself thrown in the world of concrete realities, and whose decisions are not completely independent of these realities. Albeit, man is thrown factually into the world without his consent; he is nevertheless, not determined to act according to some pre-ordained plan. Heidegger believes that human persons are free beings with a plethora of possibilities which they alone can unravel and attain. In fact, it is only when man assumes responsibility for his actions; when he overcomes his anxiety or *angst,* his fear of death, and lives in accord with his conscience, that he passes from in-authenticity to authenticity.

The concepts of freedom and determinism are not conceived in the same way by all Africans. Albeit, for example, among the Yoruba of Southwestern Nigeria, decision making is rooted in community customs and beliefs, individual opinions are equally never neglected. And in some instances, as observed by Fagbemiro and Adebamowo (2014), the individual may not even ask the community to take part in a research enterprise.

4.1.4 The Hermeneutic Phenomenological Task

Man's life, for Heidegger, is a 'this-ly', that is this individual conducting this study, this way, at this time and place, and in this mood. Human beings and the world are inextricably related in cultural, social and historical contexts. Any new endeavour always rubs up against what 'is'. Our very understanding of reality is always imbued with certain experiences and situatedness. Smythe and colleagues (2008) expressed this point well when they made the claim that to research in the Heideggerian way is to recognize that one is never outside his study, his whole being and

way of knowing are always involved. This same point was also expressed by Kafle (2011) when he argued thus:

> In using hermeneutic phenomenological approach, we accept the difficulty of bracketing. To overcome this difficulty we acknowledge our implicit assumptions and attempt to make them explicit. In addition, we accept the notion that there may be many possible perspectives on a phenomenon, like when we turn a prism, one part becomes hidden and another part opens. Hermeneutic avoids method for method's sake and does not have a step by step method or analytic requirements. The only guidelines are the recommendation for a dynamic interplay among six research activities: commitment to an abiding concern, oriented stance toward the question, investigating the experience as it is lived, describing the phenomenon through writing and rewriting, and consideration of parts and whole.

Heidegger does not believe that there are presuppositionless perceptions. For him, our perceptions have certain historicalities or foreknowledge behind them. He rejects the transcendental phenomenological assumption that our view of reality can be separated from the experiencer's cultural and historical context. Similarly, he avers that all research findings are laden with pre-structures and assumptions. These assumptions are integral part of understanding why we do what we do. We must become aware of these historicalities. It is only then that we may proceed to question how they may impact on the research process.

In the same vein, the willingness to return incidental findings, observed amongst study participants from the 19 studies, has certain historicality behind it. Heidegger is asking us to make explicit this implicit historicality. The hermeneutic phenomenological proposal aims at bringing this historicality to the fore so as to begin to interpret its implications for scientific research. Put differently, Heidegger's hermeneutic phenomenological exploration of this disposition would allow scientific research to assert itself and its own truth against researchers'; IRB chairs'; research participants' etc., historicality. There are two key hermeneutic phenomenological tasks for this essay. We are challenged to remember that the disposition to return incidental findings has been influenced by certain historicality and experience. This willingness to return is not a happenstance. We must unravel this historicality. Hermeneutic phenomenology tasks us to study the concealed experience behind this disposition. While unraveling this experience, we are challenged not to be consumed by this historicality so as to prevent research from speaking for itself, and asserting its own truth against the historicality influencing the disposition to return incidental findings. The key hermeneutic phenomenological question thus, is, "What is this historicality behind the disposition

to return incidental findings in genomic research?" This question is a core question of hermeneutic phenomenological method. Beyond this question, we would also ask; "What impact would this (returning incidental findings) have on scientific research? In other words, the use of hermeneutic phenomenological approach would be directed to a two-fold end: the unraveling of the historicality behind the willingness to return incidental findings in genomic research and secondly, an interpretative explorative impact of returning incidental findings in genomic research.

4.2 Explicating the Implicit: A Hermeneutic Phenomenological Unraveling

The principal objective in this section of the work is to unravel the historicality behind the disposition to return incidental findings in genomic research. We defined research already in this essay as a systematic investigation designed to contribute to generalizable knowledge (Levine, 2003). The goal of research is to seek out ways to improve the quality of human life, society and knowledge. As result, it is the human person; human life and knowledge of the environment that research seeks to enrich and improve. The beneficiaries of research, directly or indirectly, are always human beings. The greater part of the knowledge that is generated, or in the case of healthcare research, the cure that is discovered in research, is directed to the good of human persons and society.

Notwithstanding the great positive impacts on human life and society, research has sometimes been used to destroy human life. Human history is replete with unethical uses of human subjects in research. The Nazi experiments during the Second World War (1945-1949)[15] (Grimes et al., 2009), the Tuskegee syphilis trial (1932-74)[16], the 1954 Thalidomide experiment[17] (Kim &

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[15] Many horrific experiments were conducted by Nazi physicians and scientists, such as "infecting non-voluntary participants with malaria, freezing them for frostbite research, performing pressurization experiments with high altitudes, exposing their bodies to various industrial materials, and introducing them to various deathly gases, bacterium, viruses, and poisons. The scientists who were responsible for these horrenduous acts were tried in Nuremberg and appropriately sentenced after trials.

[16] This is another harrowing example of abuse of human subjects in research. Some poor, illiterate African American farmers were deceived and denied proper treatment for syphilis. Critical information about the study as well as information necessary for making informed decision was equally not made available to the subjects. Many of the research subjects suffered needless pain and died as a result. The horrific study led to the establishment of Institutional Review Boards and the formulation of ethical guidelines for a principled research known as the Belmont Report. The Belmont Report specified key principles for an ethical research with humans and they include respect for persons, beneficence, and justice.

[17] The Thalidomide experiment involved the use of drugs which was found to cause deformites in fetus. Many of those who took the drug claimed that they did not know they were taking experimental drugs. About 12,000 infants were born deformed because their mothers took the drug.

Scialli, 2011), the Willowbrook study, the Laud Humphreys' Tearoom study[18], etc., are harrowing examples of this abuse. etc. As a result of these horrifying studies the question became that of how to protect human subjects who participate in research from abuse.

In response to this question, several ethical codes were formulated. They include the Declaration of Helsinki (1964), which specifies how informed consent is to be obtained; the Common Rule (1970), which specifies conditions for using government funds for research involving humans; Council for International Organizations of Medical Sciences Guidelines (CIOMS), to mention but a few. Our hermeneutic phenomenological approach informs us that the willingness of researchers, IRB chairs and personnel to return incidental findings could be interpreted within the context of the desire to protect human subjects who participate in research.

In Nigeria, the immediate cause of a similar regulation, which developed into 2007 National Code of Health Research Ethics, was the 1996 Pfizer CSM Trovan trial. Institutional Ethics Committees (IEC) have been set up since then, to maintain oversights of research projects and ensure that human autonomy and dignity are respected; principles of non-maleficence, beneficence and justice properly entrenched.

The hermeneutic phenomenological unraveling of the favorable disposition to return incidental findings in genomic research thus, shows that behind this willingness to return is a desire to protect research participants from abuse. This desire has been necessitated by the previous history of abuse of human subjects who participate in research. A significant few from the reviewed studies indicated that returning incidental findings would demonstrate researcher's respect for research participants, promote their autonomy and encourage them to participate in future researches. Furthermore, by returning incidental findings, the researcher will be fulfilling an important duty of maximizing benefits to subjects and reducing their exposure to risk. From Kantian and utilitarian perspectives, this would ensure that participants are not used as mere means to an end, and that their happiness and well-being are optimized at all times.

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[18] Some ethical issues in Humphreys' study of men who engage in impersonal sex include the fact that many of these men never knew he was a researcher; their voluntary consent to participate in the study was never sought. Humphreys study took place at time when it was illegal for men to engage in gay sex. There are arguments that if the police had laid their hands on Humphreys' data and discovered the identities of the men involved, they would have been severely stigmatised or their family lives ruined, or even imprisoned. Many scholars claim that his most ethical violation is the way he masquareded himself as a 'watch queen' at the tearooms and went to the mens' homes on a false pretext, invading their privacy.

Beyond explicating the implicit historicality behind the willingness to return incidental findings, we must also explore the implication of returning incidental findings for scientific research.

4.3 Impacts of Returning Incidental findings on Scientific Research

We observed in our systematic review that there is an overwhelming dearth of empirical studies on the impacts of returning incidental findings and research results in general on scientific research. The implications for research enterprise need to be further empirically explored. We recommend more studies in this direction. Some theoretical implications have been highlighted by different scholars. These implications are enumerated below:

I. It will distract researchers from research aim and objectives
II. It will turn research into clinics
III. It will be financially burdensome
IV. It will discourage researchers and sponsors
V. It may burden research with legal liabilities
VI. It will significantly harm research etc.

Within African setting, returning incidental findings, especially findings of misattributed paternity, may lead to loss of personal and community identity. And since an African is a being amongst other beings, this may great psychological effects on the individual. Discrimination and stigmatization may also result. For these reasons, genomic skeptics would argue that creating an obligation whereby researchers routinely return incidental findings would cause harm participants. It would also stifle research progress or effectively bring about the demise of scientific research. Yet human participants in research must be protected. The hermeneutic phenomenological approach therefore, brings us to an impasse between two ethically competing decisions: i) the need to protect human subjects who participate in research and, ii) the need to ensure the advancement of scientific research. This impasse can be rephrased from Kantian perspective as follows:

a) How do we ensure that human subjects who participate in research are not used as mere means of advancing scientific research?

b) How do we secure the future of scientific research while seeking to protect human subjects?

4.4 Resolving the Impasse: A Hermeneutic Phenomenological Proposal

From the hermeneutic phenomenological point of view, the question, "Should researchers be obliged to return incidental findings in genomic research?", does not give in to easy answer. The question effectively leads to conflicting situation between two equally important ethical duties: duty to ensure that research funds and resources are directed to research ends, and the duty to reduce/prevent harm to research participants or avoid seriously jeopardizing the health of participants. This impasse is effectively a dilemma. Creating an obligation whereby researchers return incidental findings poses a serious ethical dilemma. A dilemma of this sort cannot be simply resolved by a "Yes" or "No" answer to the question posed. The following case illustrates this point:

> A family, Mr and Mrs P with their 11 yrs old son, volunteered to participate in a genetic association study for autosomal recessive disorder (Tay Sachs). They appear really motivated to participate in the study. Their son was born with the disorder. It is established that both parents must be carriers of the trait in order for the condition to be passed on to the child.
> Upon conducting a genetic test, the researcher discovers that the father is not a carrier. This can only mean one thing; the husband is not a biological father. Neither Mr. P nor Mrs P gave any indication in the consent form, that the boy is not their biological son. The testing was not done to establish paternity. What should the researchers do?

Non-disclosure of this information may result in the following outcomes: the fiduciary relationship the family has with the researcher would be gravely affected if they discover the information in the future or raise legal liabilities for the researcher. Disclosure may equally result in the following outcomes: psychological distress to Mr P, the bond in the family may be permanently severed.

Generally, returning incidental findings may stifle research progress while refusal to return may also cause research participants grave harm, especially if the findings are clinically actionable. The hermeneutic phenomenological challenge is that of ensuring that the good is ultimately done, and harm to research participants and research is significantly reduced. Given the overwhelming ethical difficulties raised by the question, "Should researchers be obliged to return incidental findings?" we would caution against obliging researchers to return incidental findings. The United States Bioethics Advisory commission already recognized in her recent report that it would cost a

fortune to return incidental findings (United States, 2013). Research is expensive already, and thus, should not be made even more expensive. Genomics skeptics are right in their argument that obliging researchers to return incidental findings would discourage scientists from conducting research. Researchers may also become dishonest about their findings, especially if they realize that they cannot afford the cost of returning incidental findings.

This position is not the same as saying researchers should not return result. We do agree with some genomic libertarians who argue that life-saving information should not be withheld from research participants. Accordingly, we recommend that researchers should be encouraged to return incidental findings when doing so would not harm scientific research nor stifle the development of research. In other words, researchers should be encouraged to return if it is financially convenient to do so; the results have been validated; clinically actionable or show serious life threatening condition.

Some other factors such as culture, religion etc., may equally affect how researchers or research personnel manage incidental findings in genomic research. For example Gordon and Paci (1997) have shown that the candid, individualistic 'American approach' to truth-telling to patients (and research participants) would be viewed by many Italians as 'very harsh, irresponsible, lonely and naïve'. In other words, cultural beliefs can complicate issues. As a result, it is sometimes preferable, as proposed by Odebunmi (2011), to stall information, or veil it, until the researcher or research personnel has adequate information about the research participants' beliefs. The researcher may also use forecasting to drop enough hints or paint other scenarios, to see how research participants would react to them (Odebunmi, 2011). Given the reality that research participants may react differently to research results, we recommend that further study should be carried out on the subjective state of research participants, with a view to identifying the indicators -- about the subjects receptiveness -- to watch out for when disclosing information to them.

Open consultations with community where the research took place, as well as consultation with colleagues in the research community are equally advised. Researchers may want to find out how many of their colleagues have had to manage incidental findings in their studies. How did they manage these findings? What were the reactions of the research participants? How did it affect their scientific research? The experiences of their colleagues may give individual researchers faced with the challenge of managing incidental findings some indications of what the reaction of their research participants may be, they cannot guarantee that their research participants would react in

the same way. As a result of this, we recommend that more empirical studies be carried out to explore other factors – gender, economic or level education -- which may affect the return of incidental findings in genomic research. We also recommend that studies should be carried out to explore the impact of returning incidental findings on research and research participants.

Finally, the hermeneutic phenomenological approach shows that the effective management of incidental findings, is a product of a number of things. This management is not the same as saying "Yes" is right and "No" is wrong. Rather, it is a product of the consideration of research historicalities, of morally relevant issues and of careful evaluation of possible outcomes and their impacts on research and/or research participants; as well as investigation into the research participants' cultural or religious beliefs to mention but these. We agree with Sokol (2006) that dilemmas, such as the one created by incidental findings in genomic research, remind us of the need to set up procedures to resolve the issue prior to the emergence of the problem. A plausible solution would be to inform research participants at the outset, of the possibility of incidental but potentially important findings and to ask them if they would like such findings to be revealed. This hermeneutic phenomenological proposal, is for researchers to have an original position with their research participants. As stated already in this essay, researchers should discuss with research participants (as well as community leaders for research in African settings) before obtaining consent the following:

I. The details of the study
II. The risks, limitations, and benefits of the study
III. Privacy/confidentiality issues affecting participation in the study
IV. The voluntary nature of participation
V. The potential consequences related to results, including: (a) impact on health; (b) emotional and psychological reactions; (c) treatment/prevention options; and (4) ramifications for the family
VI. Possibility of finding other conditions not being tested
VII. Whether the patients would like to be told.

Conclusion

In the essay, we set out to systematically review the attitudes and perspectives of researchers and other stakeholders to the management of incidental findings in genomic research. In pursuing this aim, we divided the essay into four chapters. In the first chapter, we carried out a literature review of different scholarly works on genomic research. We equally defined genomic research as the study of the functions and interactions of all the genes in the genome. More importantly, we mentioned in the chapter that as genomic technologies, particularly sequencing of whole genome become more and more feasible and economically preferable in medical research, incidental findings would inevitably be a recurrent issue in genomic researches. The question of how they should be managed would therefore, also continue into the future. The scope of genomic research, as well as the broad types such as gene testing, gene therapy, reproductive genomics and pharmacogenomics was equally highlighted. The chapter concluded with an examination of issues raised in genomics.

In the second chapter, we clarified key concepts and ideas in incidental findings management. In the chapter, we defined incidental findings as an unanticipated finding, with or without clinical significance, about a research subject, discovered in the process of a systematic and methodic analysis of data for findings related to the aim and objectives of research study. Two positions were identified in this chapter; (i) genomic libertarians who argue that researchers should be required to return validated and clinically significant incidental findings to research participants. (ii) genomic skeptics who, following the reasons of financial burden, the risks of harm to research participants, legal liabilities, practical implementation issues, and therapeutic misconception, maintained that creating an obligation whereby researchers routinely return incidental findings would negatively impact research enterprise or discourage sponsors. In place of creating an obligation to return, Beskow and colleagues proposed that a summary result may be presented to the general public (Beskow et al., 2012). A summary result, they argue, albeit not a substitute for meeting the challenges of incidental results may serve as a powerful and effective means of demonstrating respect for research participants and appreciating their contributions to research.

The third chapter was a review of various studies on the management of incidental findings. Using certain filters, we identified nineteen articles and entered them into EndNote X6. For reasons of standardization and uniformity, we developed a data extraction form. The extracted data were

processed using IBM SPSS version 20. The general characteristics and results of analyses were presented under the following endings:

i. Description of incidental findings.
ii. Incidental findings management preference.
iii. Conditions for returning incidental findings.
iv. Factors affecting return of Incidental findings.
v. Who should return incidental findings?
vi. To whom should incidental findings be returned?

In chapter four, which is the final chapter, we carried out a hermeneutic phenomenological discussion. Hermeneutic phenomenology is Heidegger's greatest contribution to philosophy, and it is a method that is mainly used to investigate the meaning of lived experience. As Lindseth and Norberg (2004) put it, "the results (of this hermeneutic phenomenological exploration) help us and others gain insights about our world and ourselves; and see our world and us in a new perspective." Similarly when applied within the purview of qualitative studies, hermeneutic phenomenology is useful in helping researchers to use their fore-knowledge to gain meaning from their studies in workable ways. It also helps them to improve science. But unlike previous applications of hermeneutic phenomenology where the sole concern is on helping researchers to use their foreknowledge to improve practice, this essay goes a mile further to help researchers understand the worldview or historicality behind an observed reality. This is the first time this approach would be used this way.

The hermeneutic phenomenological approach has equally shown that the debate on the management of incidental findings would continue into the future. In other words, the debate is far from over, and the debate in reality is about how to resolve a dilemma. Here, we must state that there are no straight forward answers to how incidental findings should be managed. Empirical studies have equally not satisfactorily explored important questions such as: "Who should return the findings?" "Who should receive the findings?" "Should hereditary findings be communicated to third parties?" "What is the length of duration to return?" "What are the reasons for disclosure?", etc. These are important questions which would generate controversies in the future. This study strongly recommends that more empirical studies which would address these questions should be carried out. Ultimately, the impasse created by the debate on incidental findings management

reminds us of the need to be more proactive in our approach. Researchers and research participants need to have an original position on how to handle incidental results before they emerge.

This essay argues that when there are no original positions[19] between the researcher and research participants, researchers should not be obliged to return incidental findings. Significant harm may arise if researchers are obliged to return incidental findings. It may distract researchers from research aim and objectives, thus negatively impact research enterprise. The financial implication of returning incidental findings is high. Obliging researchers to return incidental findings may discourage research sponsors or encourage researchers to be dishonest about their research findings. Researchers should, however, be encouraged to return incidental findings when doing so would not distract them from research objectives or put them in financial comatose.

Before returning, researchers must also consider whether knowledge of the incidental information would not cause research participants considerable and preventable harm. Herein, this essay asserts that harm is not limited to research enterprise alone but also includes distress to research participants or breach of trust. As Sokol (2006) argued, the prevailing view in the Western world that patients, by extension research participants, should or would like to be told the truth would be supported by only a few in China, Singapore, and one may add in some countries in Africa. Important cultural and religious worldviews, marital status, gender to mention a few, may complicate ethical evaluation of the risk-benefit ratio of returning incidental findings. There is so much empirical uncertainty that research participants would benefit rather than harmed, from receiving incidental findings with significant health implication. For example how would research participants react to the news that they have serious but untreatable health condition? It is likely they would be distressed from knowing that their condition cannot be treated. The knowledge may kill them faster than the condition itself. Some of these research participants may view this information as a disservice to them. Some may even think that their condition was caused by participating in research, and thus, lose faith in research enterprise. For these reasons, truth telling may not always be the best policy. Important moral considerations such as avoiding considerable harm to research participants should also determine whether incidental findings should be disclosed to research participants.

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[19]Original position, developed by John Rawls, is a position when free and equal contracting parties jointly agree upon, and commit themselves to certain principles of justice before the commencement of the contract relationship.

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APPENDIX ONE

DATA EXTRACTION FORM

Review title or ID
Name of Student

General Characteristics

Report title(Title of Paper or article)	
Author ID/Year	
Authors contact details	
Date of Publication	
Reference Citation	
Type of Publication	
Country of Origin	
Source of Funding	

Study and Subjects' Characteristics

1) Context ☐ Research Setting ☐ Clinical Setting
2) Study Type ☐ Involving Participants ☐ Documents Review
3) Aim of Study
4) Emphasis
5) Population Description ☐ Geneticists (Professionals and Specialists)

☐ Researchers

☐ IRB chairs

☐ IRB professionals

☐ Biobankers

☐ Participants/Patients/Public

☐ Document

6) Sample Size

Result

Identifiers

■ Majority

■ Minority

■ Fairly Divided/No clear majority

■ Unclear Data/Provided No data or said No

GIFs - Incidental findings in genomic research.

1) Understanding of GIFs-
2) Encountered GIFs before? ☐ Yes ☐ No
3) GIFs in genomic studies would increase overtime: ☐ Yes ☐ No
4) Suggestions for GIFs in Genomic Study:

☐ Researchers should anticipate GIFs

☐ General policy/plan should be included in consent processes

☐ No general policy/plan. Evaluate individual cases

☐ Researchers do not have the responsibility to look for GIFs

☐ Offer genetic counselling before returning GIFs

☐ Override subject wishes if condition is preventable and actionable

5) How should GIFs be handled?

☐ Do not return GIFs generally

☐ Return GIFs

6) What type of information about GIFs should be included in consent documents for genomic studies?

☐ Indicate possibility of clinically non/significant GIFs

☐ GIFs management plan should be outlined

☐ Give a general understanding of how GIFs may have clinical significance

☐ Explain potential risks and benefits of disclosing GIFs

☐ Elicit participant disclosure preferences

☐ Provide simple definition of GIFs

☐ Specify duration of duty to disclose

7) Length of duration of obligation to return

☐ Project period

☐ Ongoing access to database

☐ Indefinitely

☐ Unclear Data

8) What type of GIFs should be returned? ☐ Analytically Valid Results

☐ Conformity to applicable Laws

☐ Subject has not opted out of receiving

☐ Reveals serious health condition

☐ Clinically actionable/significant

☐ GIFs with personal value

☐ Serious but untreatable

☐ Return nongenetic GIFs

☐ Return nongenetic GIFs measured at enrollement

☐ Return all incidental findings in genomic study

9) Reason for Disclosure ☐ Disclosure shows respect for research participants.

☐ Disclosure affords opportunities for preventive measures

☐ It would encourage participation in research

10) Issues in returning GIFs: ☐ Research is not clinical care

☐ Research is not conducted in labs optimized for clinical care

☐ Resource intensive and/or financially burdensome

☐ Psychological harm

☐ Infeasible and impracticable

☐ Potential legal liabilities

☐ Discrimination

☐ Privacy/confidentiality concerns

11) Who should GIFs be returned to?
- ☐ Research participants/patient
- ☐ Inform family members if gene is inheritable.
- ☐ Do not inform family members if gene is not inheritable or treatment is not available
- ☐ Inform the parent or guardian if it is a child
- ☐ Unclear/Provided No Data or Said No

12) Who should return GIFs?
- ☐ Researchers
- ☐ IRB
- ☐ Geneticists
- ☐ Subject physician/Ordering physician
- ☐ Appropriately trained personnel
- ☐ Cooperative group bank
- ☐ Unclear/Provided No data or Said No

Other information

1) Key Conclusion of Study	
2) Reference to other study	

APPENDIX TWO

Key Conclusions from Reviewed Studies[a]	
1	Researchers generally favor case by case determination of whether to disclose or not disclose GIF, while IRB chairs favor general plan in informed consent form.
2	IRB chairs are of the opinion that researchers should include plan for managing GIFs in consent processes
3	There is a continued reliance on case by case management of Genomic GIFs in the clinical setting, albeit issues such as whether there is any need to obtain patients permission prior to GIFs disclosure, when and how to inform remain unclear.
4	The public generally favor that incidental findings, with known clinical or personal values, should be returned to patients
5	The publics' interest is well aligned with the desire to be informed about potential benefits and risks before testing, promoting patient autonomy
6	Returning GIFs would require significant resources to fulfil an obligation of re-contact of subjects
7	Biobanks current policies on incidental findings management vary
8	Publicly available documents shows that biobanks are split fairly evenly on whether or not they even address return of incidental findings in genomic research
9	There was considerable concordance amongst specialists that certain conditions, if discovered incidentally should be returned. The degree of discordance observed also shows that whether in research or clinical setting reaching a consensus on what meets that threshold for disclosure would be difficult
10	The study shows that genomic researchers feel a strong obligation to offer individual research results, including incidental findings, to participants and family members, especially if the findings are clinically actionable
11	The study reveals that families undergoing exome sequencing opt for the disclosure of secondary findings.
12	IRB professionals generally favour return of validated research results if the subject desires it. However, provision of results to subjects is conditioned on a variety of factors
13	Conditions with high level of concordance among experts (genetic specialists, trained personnel, physicians etc)` represent those with the highest degree of clinical actionability and thus would be important to return as incidental findings
14	Very few documents address incidental findings, and there is very little guidance available for researchers as to how to deal with incidental findings
15	There is a growing consensus that actionable IFs should be disclosed to patients
16	Both professionals and public generally agree that GIFs should be returned, but they differ on when and to whom GIFs should be returned.
17	Nearly all cancer patients want to be informed of incidental findings related to their health
18	Most participants believed that physicians had a responsibility to disclose at least the potential of ancillary risk information
19	The majority of the researchers believe that research participants should have the option to receive at least some incidental genetic research results

Total	N	19
Table 3.4		
a. Limited to first 100 cases.		

APPENDIX THREE

UNIVERSITY OF ILORIN TEACHING HOSPITAL

Chairman:
MRS. OLAJUMOKE ANIFOWOSHE
L.L.B. (HONS) ACIArb
Chief Medical Director:
PROF. A.W.O. OLATINWO
MBBS. FWACS, MBA, AMNIM
Chairman Medical Advisory Committee:
DR. B. S. ALABI
MBBS. FWACS, FMCORL
Cert. Health Inf. Mgt.
Director of Administration:
DR. (MRS.) Y.C. AYO-BELLO FHAN
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UITH ERC Protocol Number: ERC PIN/2013/11/0129
UITH ERC Approval Number: ERC PAN/2014/01/1267

Our Ref: ***UITH/CAT/189/17[A]/644*** *Date:* ***03/01/14***

MANAGING INCIDENTAL FINDINGS IN GEOMIC RESEARCH: A SYSTEMATIC REVIEW AND HERMENEUTIC EXPLORATION

UITH Ethical Research Committee (ERC) assigned number: NHREC/02/05/2010

Name of Applicant/Principal Investigator: OLUKUNLE CORNELIUS EWUOSO.
Address of Applicant: Dept. of Clinical Sciences/Surgery (Biothics) University of Ibadan
Date of receipt of Application : 20/12/2013
Type of Review: Expedited Review
Date of Full Committee Decision on the Research: 06/01/2014
Date of Full Committee Approval: 06/01/2014

Notice of full committee Approval

I am pleased to inform you that the research described in the submitted protocol, the consent forms and other participant information materials have been reviewed by the UITH Ethical Review Committee (ERC) and given full Committee approval.

This approval dates from 06/01/2014 to 05/01/2015 You are requested to inform the committee at the commencement of the research to enable it appoint its representative who will ensure compliance with the approved protocol. If there is delay in starting the research, please inform the ERC so that the dates of approval can be adjusted accordingly.
Note that no participant accrual or activity related to this research may be conducted outside these dates.

The UITH ERC requires you to comply with all the institutional guidelines and regulations and ensure that all adverse events are reported promptly to the ERC.
No changes are allowed in the research without prior approval by the ERC. Please note that the ERC reserves the right to conduct monitoring/oversight visit to your research site without prior notification.

Thank you.

PROF. O.T. ADEDOYIN MBBS (IL.), FWACP (Paed.), ASN/ISN Fellow, Cert. HP&M
Chairman, UITH Ethics Review Committee. (ERC)