ETHICAL ASPECTS OF GENETIC INFORMATION ABOUT HEREDITARY CANCER SYNDROMES.

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

December 2015

DEDICATION

I dedicate this thesis to the hundreds of patients, usually known to me only by a name and number, where my diagnosis of a malignant tumour often serves as a death sentence, with the most profound and traumatic effects on their life, and even more so on those who know them as a beloved father, mother, child ……

ACKNOWLEDGEMENTS

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SUMMARY

The practice of medicine is constantly changing as technology enables us to redefine our understanding of the pathophysiological basis of disease. These new medical techniques and technologies often raise new moral and ethical dilemmas, forcing us to constantly reflect on our practice of bioethics, and to keep it relevant if we do not want to create a bioethical void.

Neoplastic diseases, like colon and breast cancer, are sometimes associated with genetic abnormalities, some of which are inherited. A number of hereditary cancer syndromes have been identified, including Lynch syndrome.

Two issues, related to scientific developments in the fields of histopathology and molecular pathology, and both of which are of importance to the histopathologist and the clinician/genetic counsellor, are discussed in this thesis.

The first issue relates to the apparent merging of the concepts of the genotype and phenotype, and the consequences of such a unified concept. I believe that the staggered approach to obtain consent for the examination of a histopathology specimen, is outdated in view of the availability of a whole range of modern techniques and technologies, which allow us to analyse any point along the genotype – phenotype spectrum. Some investigations straddle the concepts of genotype and phenotype, and it is not always clear whether these investigations may be performed without the specific consent of the patient. If we accept a merged concept of the genotype and phenotype, I believe best clinical and ethical practice would be to obtain specific informed consent for the histopathology examination of the specimen in advance. This consent must be comprehensive and inclusive of all investigations, including genetic testing for both somatic and germline mutations.

My second argument is based on the ownership of genetic information related to hereditary cancer syndromes. It does sometimes happen for various reasons, including the fear of stigmatisation or discrimination, that the index patient refuses to disseminate this information to his family. The ethical dilemma then arises whether the healthcare worker can divulge this information without the necessary consent and against the index patient's

express wishes. This dilemma hinges mainly on two ethical issues, i.e. confidentiality and privacy.

An analysis of the professional guidelines as well as current legislation and case law, is supportive of my opinion that the right to confidentiality and privacy is not absolute, and that this information may be divulged to at-risk family members.

The ethical and moral implications are analysed from the perspective of the three main ethical and moral theories – virtue ethics (especially the virtue of *phronesis* as basis of an ethics of responsibility), utilitarianism and deontology – as well as the principles of biomedical ethics as formulated by Beauchamp and Childress.

I believe that there is professional, legal and also moral justification to divulge important and potential life-saving information regarding the possibility of a hereditary cancer syndrome to at-risk family members. In fact, there is a duty to do so.

OPSOMMING

Die praktisering van geneeskunde verander gedurig soos tegnologiese vooruitgang ons begrip aangaande die patofisiologiese basis van siektes herdefinieer. Hierdie nuwe mediese tegnieke en tegnologie skep dikwels nuwe morele en etiese dilemmas. Dit forseer ons om gedurig te reflekteer oor ons praktisering van bio-etiek, dit relevant te hou, en so te verhoed dat ‘n morele leemte ontstaan.

Neoplastiese siektes, soos kolon- en borskanker, is soms assosieerd met genetiese abnormaliteite, waarvan sommige daarvan oorerflik is. ‘n Aantal oorerflike kanker sindrome is reeds identifiseerd, insluitende Lynch sindroom.

Twee aangeleenthede wat spruit uit die wetenskaplike vooruitgang in die mediese dissiplines van histopatologie en molekulêre patologie, en wat beide van belang is vir die histopatoloog en die klinikus/genetiese raadgewer, word in hierdie tesis bespreek.

Die eerste kwessie spruit uit die skynbare samesmelting of eenwording van die konsepte van die genotipe en fenotipe, en die gevolge van sodanige verenigde konsep. Ek glo dat die stapsgewyse benadering om toestemming te verkry vir histopatologie ondersoeke oudmodies is, in die lig van die beskikbaarheid van ‘n hele reeks moderne tegnieke en tegnologie, wat ons in staat stel om enige punt op die genotipe-fenotipe spektrum te kan analiseer. Sommige ondersoeke oorbrug die konsepte van genotipe en fenotipe en dit is nie altyd duidelik of die ondersoek uitgevoer mag word sonder die spesifieke toestemming van die pasiënt nie. Ek glo dat as ons ‘n verenigde konsep van die genotipe en fenotipe aanvaar, dit dan die beste kliniese en etiese praktyk sal wees om spesifieke ingeligte toestemming vir die histopatologiese ondersoek vooraf te verkry. Hierdie toestemming moet omvattend wees en al die ondersoeke insluit, insluitende moontlike genetiese toetse vir sowel somatiese en kiemlyn mutasies.

My tweede argument is baseer op die eienaarskap van genetiese inligting wat verband hou met oorerflike kanker sindrome. Soms gebeur dit dat die indeks pasiënt weens verskeie redes, soos die vrees van stigmatisering en diskriminasie, weier om hierdie inligting deur te gee aan die familie. Die etiese dilemma ontstaan dan of die gesondheidswerker by magte is om hierdie inligting te openbaar sonder die nodige toestemming en teen die uitdruklike

wense van die indeks pasiënt. Hierdie dilemma berus grotendeels op twee etiese aspekte, naamlik vertroulikheid en privaatheid.

'n Ontleding van die professionele riglyne asook huidige wetgewing en hofuitsprake ondersteun my mening dat die reg tot vertroulikheid en privaatheid nie absoluut is, en dat hierdie inligting openbaar mag word aan die familielede blootgestel aan die risiko.

Die etiese en morele implikasies word benader vanuit die perspektief van drie belangrike etiese en morele teorieë – die etiek gebaseer op deugde (veral *phronesis* as deug en as basis van 'n etiek van verantwoordbaarheid), utilitarianisme en deontologie - asook die beginsels van biomediese etiek soos formuleer deur Beauchamp en Childress.

Ek glo dat daar professionele, wetlike en ook morele regverdiging bestaan om belangrike en potensieel lewensreddende inligting aan familielede met 'n risiko vir 'n oorerflike kanker sindroom, oor te dra. Daar is inderwaarheid 'n plig om dit te doen.

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1 Introduction

For centuries, man has been aware that some families may harbour certain familial characteristics and traits. These may manifest as unique physical or mental features covering the whole spectrum, ranging from the desired to the undesired. Some of these traits include the tendency to develop certain diseases, like cancer.

Even before the discovery of the double helix structure of DNA[1] by Watson and Crick in 1953, geneticists were able to track the inheritance of an abnormal gene by compiling a family pedigree or tree. Lacking the detailed knowledge of the structure of genes, which we possess today in the post-Human Genome Project era, the specific genetic abnormality or mutation was often unknown (Coleman and Tsongalis 2009; Turnpenny and Ellard 2012; Rooney 2009). Karyotyping of chromosomes (cytogenetics) enabled the morphological identification of chromosomal abnormalities as the underlying genetic mechanism for conditions like trisomy 21 or Down's syndrome. Molecular genetics enabled us to detect the underlying genetic abnormality in Mendelian diseases, like cystic fibrosis. Although these techniques were accurate, it was slow and expensive processes. In addition the low resolution of chromosome analysis, which may leave the deletion of 5 million base pairs of DNA undetected, as well as the limited capacity of molecular genetics to sequence more than a few hundred base pairs at a time, were all limiting factors (Urban 2015, p.545).

During the last two to three decades, technological developments in molecular medicine and pathology have opened a complete new world to scientists. New scientific techniques, like next generation gene sequencing supported by unlimited bio-information capacity, are able to generate and analyse vast amounts of genetic information rapidly and accurately. These techniques have evolved from research tools into sophisticated commercialised instrumentation, to become an integrated part in the armamentarium of most modern diagnostic pathology laboratories.

Modern science has provided humankind not only with an understanding of the concept of genetics down to the base pairs forming the structure of our DNA, but has also explored the

[1] Deoxyribonucleic acid (DNA) is a double helix molecule that carries the genetic code of all known living organisms and many viruses. It is arranged in the cellular nucleus in structures called chromosomes.

concepts and roles of other non-genetic factors, like epigenetics and the science of the "-omes" and "-omics" (Wiki Series 2011). Not only has it highlighted the important roles played by each of these fields, like proteomics (addressing the proteome[2]), metabolomics (addressing the metabolome[3]), etc., in giving physical and physiological structure to the cell and ultimately the organism, but it has also emphasised the interdependent role of all these different genetic as well as non-genetic concepts. Genes and their products are usually central to many of these new fields of interest.

Continuous developments in molecular and genetic pathology, and to a lesser extent histopathology, not only vastly expand our scientific knowledge in an exponential manner, but as in the case with many other scientific developments in the field of medicine, also result in its fair share of ethical and moral dilemmas. A well-known example is the "Scribner Shunt" in the 1960's, forcing philosophers and ethicists to formulate policies on issues like the allocation of scarce resources (Jonsen 1990, p.17). Dialysis was invented in the 1940's by Willem Kolff, but it only provided temporary relief for those patient suffering from severe renal failure. Arterial and venous access is required for dialysis, but the repeated vascular cannulation damages the vessels, and with time vascular access becomes impossible. Doctor Belding Scribner developed a shunt, or artificial vascular bypass, which is inserted in the forearm of the patient and provides a site or portal for repeated access to the vascular system. This innovating idea drastically improved the survival rate of patients with chronic renal failure, and therefore also the number of individuals requiring life-long dialysis. Unfortunately, dialysis machines were not freely available and at the Seattle Artificial Kidney Centre a committee of laypersons had to select those individuals qualifying for chronic dialysis, and by implication earmarking those eligible for survival. This group was known as the "life or death committee", or also as the "God committee". It highlighted the bioethical issues associated with the allocation of scarce medical resources and in particular its potential discriminatory effect.

Ironically, the fact that a resource is freely available, may sometimes also have a down-side. The irresponsible and often inappropriate use of highly potent broad spectrum antibiotics

[2] The proteome represents all the proteins expressed by a cell or organism, and it may vary from time to time depending on the cellular cycle or other factors, including the effect of other proteins, like hormones, on the cell.

[3] The metabolome represents all the metabolites in a cell or organism produced by the cellular processes.

has led to the emergence of highly resistant bacterial strains or "super-bugs". Antibiotic stewardship committees now monitors, and often controls, the prescription of the newer generations of antibiotics in hospitals, and patients (and their physicians) no longer have uncontrolled access to this resource.

Medicine will always be in a constant process of scientific evolution and the new available techniques and technology will often push our boundaries of competence – not only a matter of what we are able to do, but also our knowledge of the individual patient, including his genetic make-up. Jonsen (*ibid*., p.19) highlighted this interaction between scientific medical development and bioethics, by stating "the task of bioethics is, in my view, to preserve the wisdom and to remedy the weakness, in the hope of formulating a new ethics to guide the new medicine."

New technologies, like the Human Genome Project, bring with them new ethical, legal and social implications (ELSI), and these issues need to be addressed.

One of the central issues in genetics stems from the fact that genetic information is not only a reflection of the genetic make-up of the individual at stake, but also of the biological or genealogical family, and to some extent, even society and humankind. The primary aim of genetic testing, like most other modalities in medicine, is to benefit the patient. Unfortunately, it does carry risks like invasion of privacy, stigmatisation and discrimination.

In some cases, the clinical presentation and morphological appearance of a tumour may alert the pathologist and clinician to the possibility of an underlying genetic abnormality. A family history will be further supportive of the possibility of a hereditary cancer syndrome. Lynch syndrome is an example of such a condition (see annexure A for a synopsis of this syndrome).

As a histopathologist by profession and not a molecular pathologist or geneticist, I can be regarded as a "user" of the information produced by these experts. I am not a technical expert in this field, and only have a rough understanding and working knowledge of these techniques and their application to histopathology practice. The aim of the thesis is therefore more to focus on the bio-ethical implications of the knowledge generated by these analyses, rather than to comment on the technology itself.

In this thesis, a brief background of the science of histopathology and molecular pathology, as well as the significance of hereditary cancer syndromes (chapter 2), will be followed by a discussion on our changing perspective of medicine and genetics (chapter 3). This will be followed by a discussion of the concepts of phenotype and genotype (chapter 4), and the consequences of the apparent merging of these two concepts.

A review of the current ethical and legal positions on the "ownership" of genetic information will attempt to define the "playing field". This will include a discussion of the interests of different parties in an individual's genetic information (chapter 5). Ethical issues in genetic testing, including consent, confidentiality and privacy, as well as professional guidelines which may assist the health care practitioner to apply these principles and rules in everyday practice, will be dealt with extensively (chapter 6). The issue of non-disclosure, and specifically the reasons why people do not want to disclose genetic information will be dealt with in chapter 7. A review of the relevant legislation, professional guidelines and case law will be given in chapter 8.

In the latter part of this thesis, I will formulate and state my position on the following two issues. Firstly, I will argue that as a result of scientific developments the concepts of genotype and phenotype have merged into one entity, and that our consent procedures for the surgical removal of cancer specimens must allow the comprehensive histopathology analysis thereof to enable the maximum generation of information (chapter 9).

Secondly, the ethical and moral approach to address the bio-ethical dilemmas related to genetic testing, and especially the ownership of information, will be discussed in chapter 10. An approach based on virtue ethics, and in particular an ethics of responsibility based on the virtue of *phronesis*, will be promoted as the most appropriate theory. Three other theories - utilitarianism, deontology and the four principles of Beauchamp and Childress - will also briefly be referred to, to identify potential conflict and/or coherence amongst the different theories. This thesis concludes with a few words on the future of genetic testing as part of the rapidly evolving molecular diagnostic science, and its role in a more holistic approach in individualised medicine, as well as a final brief summary of my position (chapter 11).

2 Scientific background

To be able to understand where we are at present, we need to know where we are coming from in our journey through medical science. A brief discussion of the background of the development of histopathology and molecular pathology is therefore appropriate.

2.1 Histopathology

Histopathology is the discipline in medicine dealing with the examination of tissue samples. The early medical practitioners were aware that certain tumours or neoplasms grow as lumps with a crab-like *(cancer)* infiltrating appearance, ultimately leading to the demise of the patient. Inventions and innovations, like the development of the microscope by Antoni van Leeuwenhoek (1632 – 1723) and the use of dyes to stain tissue sections, opened a vast new field for the examination of these tumours, as well as other organisms including bacteria and fungi. The foundations of histopathology were finally laid when Rudolph Virchow (1821 – 1902) published *Die Cellularpathologie* in 1858, describing medical conditions on cellular level and establishing a link between the morphological findings and the disease (Rooney 2009; Strathern 2005).

Although histopathology also includes the diagnosis of inflammatory and non-neoplastic disease processes, like acute appendicitis and skin conditions, the examination of tumours or neoplasms is a very important field of practice for the histopathologist. Not only is it important to differentiate between benign and malignant tumours, but also to assess the possible prognostic features of a malignant tumour. The latter include the grading of the tumour, which reflects the degree of differentiation of the tumour cells, as well as invasion of blood and lymphatic vessels, which indicates a higher risk for metastases elsewhere in the body (Kumar *et. al*. 2015; Rosai 2011).

For many years, the information produced by histopathology examination was limited to the light microscopy appearance of the tissue and the individual cells. Electron microscopy allowed a higher magnification of the structure of cells, but to determine the functionality of

a cell was often a matter of inference. For instance, a cell with large amounts of keratin intermediary filaments was regarded as an epithelial cell, while a cell containing myofibrils represented a muscle cell with the ability to contract.

The antibody-antigen reaction forms the basis of many clinical laboratory techniques. A major development in the scope of histopathology over the last 30 - 40 years was the application of this technique to histopathology, where specific antibodies bind to targeted tissue antigens, and can then be marked for visualisation through the microscope. This technique is called immunohistochemistry (Taylor and Cote 2006; Dabbs 2014).

Immunohistochemistry enables us to evaluate a number of different aspects of a cell: the line of origin, function, expression of genetic products, like proteins, as well as the proliferative activity. By looking through a bright-field microscope, we are now able to visualise both the structural and functional components of a particular cell. In other words, we are now also able to visualise the expression of some of the genetic characteristics of a particular cell.

2.2 Molecular pathology

The second important development since the last decades of the previous century is the application of molecular pathology techniques in histopathology (Turnpenny and Ellard 2012). Although there are some differences in the concepts of molecular pathology and genetic pathology, the two terms will be used interchangeably for the sake of this discussion.[4] Molecular pathology enables us to identify abnormalities or mutations in the DNA sequence, which may translate into genetic abnormalities ultimately expressed as a disease. This rapidly expanding field of science and medicine is associated with an exponential increase in our knowledge about different tumours and diseases; not only whether there is a hereditary risk, but also to establish the best treatment option and to assist in the prognostication of a tumour.

[4] As molecular and genetic pathology involves so many different pathology sub-disciplines, more and more authors prefer the term “molecular diagnostics”.

Different techniques can be used to analyse genetic abnormalities; these include the use of genetic probes and the sequencing of the genetic code. Techniques, like fluorescent in-situ hybridisation (FISH), are relatively simple to use, whilst others require more specialised platforms and expertise. The FISH technique is based on the use of fluorescein-marked probes to determine the presence or absence of specific DNA sequences on chromosomes, which is then visualise by means of a fluorescent microscope.

What is the significance of all these developments in histopathology? By looking down his microscope, albeit with the use of antibody-antigen reactions and genetic probes, the modern day histopathologist can now analyse the morphological structure, function and even the genetic abnormalities of a cell. As the type of tumour is a function of the underlying genetic abnormality or mutation, there is a real possibility that the future role of histopathologists in the management of tumours may be limited to the reporting on the adequacy of resection margins, with molecular pathology dealing with the diagnosis and classification of the tumour itself (Louis *et. al*. 2014). Histopathology, like medicine in general as viewed by William Osler, is not an exact science, but rather an art, based on science (Beam 1985, p.17). Interpersonal variance amongst histopathologists is a well-known problem in the diagnosis and especially the classification of tumours (Rosai 2011). A genetic-based classification system will solve this problem.

2.3 Somatic mutations

Genetic mutations can be either germline or somatic mutations (Turnpenny and Ellard 2012). Any tumour has the ability to undergo somatic mutations as part of the ongoing process of biological transformation and anaplasia[5]. Some of these mutations may for instance increase the ability of the tumour cells to invade blood vessels and therefore the risk of haematogenous spread or metastases. It is important to realise that these changes at molecular level are unique to that particular tumour; it was neither inherited nor will it be transmitted to the offspring of the patient – it is therefore somatic.

[5] Anaplasia refers to the loss of differentiation by malignant cells. During this process it loses the characteristics of the normal mature cell.

The presence or absence of some mutations will also predict the response to so-called targeted drug therapy. These mutations are used to predict the prognosis and treatment response (pharmacogenomics[6]) for that particular tumour. Some of these drugs, like Herceptin for the treatment of breast cancer patients with Her-2 receptor overexpression, are expensive, but relatively commonly used in oncology practice and paid by most healthcare funders in South Africa, although there was initially some objection from healthcare funders. Other newer targeted oncotherapy drugs, like those for colorectal cancer, is usually a very expensive treatment, and the financial implications of this treatment result in its own ethical and moral dilemmas. Firstly, from a health care funder's perspective (including the public health sector) a utilitarian can argue that it is better to invest the money into screening programmes, like colonoscopies, with the potential to save the lifes of a couple of people, rather than paying more than R500 000 for the treatment of a single patient, just to add a couple of weeks or months to the survival period. Secondly, the question can also be asked whether it is ethical to perform an analysis to determine whether a patient is a suitable candidate for a particular drug, knowing in advance that neither will the patient be able to afford this expensive treatment, nor will it be covered by the healthcare insurance? In this scenario, knowledge of this information is worthless. Having this knowledge, but not being able to use it to your advantage due to financial constraints, may create feelings of frustration, despair and even discrimination.

To prevent the generation of potentially inappropriate or unnecessary information, the application of genetic testing to generate pharmacogenomical information needs a "gatekeeper". The most appropriate person is the oncologist who knows best whether a patient would either be a suitable candidate who may benefit from a particular drug, or would be in a position to afford it. Having said that, section 6 of the National Health Act (2003) places an obligation on the healthcare practitioner, stating specifically that a user must be informed of "the range of diagnostic procedures and treatment options generally available to the user" (my emphasis). Most clinicians will agree that the word "generally" is open to interpretation, and may not necessarily include treatment like pharmacogenomics. The oncologist is in the best position to decide what is the most appropriate information to

[6] Pharmacogenomics: the application of genetic information to determine the susceptibility of cancer cells for a specific drug or an individual's genetic encoded response to a particular pharmacological drug.

be conveyed to the patient, and to guide the pathologist to perform the necessary tests to obtain information of a pharmacogenomic nature.

2.4 Germline mutations

On the other hand, germline mutations are inherited and transmitted from one generation to another, usually according to Mendelian principles (Turnpenny and Ellard 2012). It therefore not only reflects the genetic profile of that particular patient (and tumour), but also that of the parents and even the extended family. To complicate matters even more, other genetic factors like penetrance[7] and expression of variance[8] will also play a role. Having an abnormal gene may therefore not necessarily result in the development of any, or some, of the clinical manifestations of a disease.

Some diseases and syndromes are monogenic in origin, while others are polygenic with more than one genetic abnormality at play. Most diseases however, are multifactorial in origin with genetic, environmental, dietary and other epigenetic factors all playing a role (Kumar *et. al*. 2015). In this latter group, the genetic factors are so integrated with and diluted by the other factors, that it is almost impossible to calculate and predict the hereditary risk to develop a particular disease in an objective and scientific manner. These diseases therefore seldom present as an ethical problem. Monogenetic, and to a lesser extent polygenetic, diseases are different as the disease or syndrome can be reduced to a single mutation, which can be transmitted (and traced) from one generation to another.

2.5 Hereditary cancer syndromes

Some cancers arise in individuals who carry a germline mutation (Turnpenny and Ellard 2012; Kumar *et. al*. 2015; Rosai 2011). The genetic predisposition, and therefore the ability to identify individuals who may be at risk, has been well established for cancers of the

[7] Penetrance: the percentage of people with the genetic abnormality who will develop the disease/tumour.
[8] Variance of expression: the various phenotypical expressions of the genetic abnormality, like different types of tumours in Lynch syndrome.

colon, breast, stomach, uterus, ovary, thyroid as well as other sites. Lynch syndrome (see annexure A) is a well-known example of such a syndrome (Vogelzang 2013). These germline mutations may result either in the activation of a promoter gene/cancer-predisposing gene or the loss of a cancer suppression gene, as well as in the abnormal coding for proteins and other cellular components.

The identification of such a cancer-related mutation enables the geneticist to offer predictive genetic testing to the other family members, who may still be asymptomatic or in a pre-clinical stage. It creates the opportunity to institute preventive measures through "targeted surveillance, chemoprevention and risk-reducing surgical options" (Harris *et. al*. 2005, p.301).

It is also important to consider those cases where there may be a high clinical suspicion of a hereditary cancer syndrome, but genetic analysis fails to detect a genetic abnormality. Even a "negative" result may not be that straightforward.

First, it may be a false negative result, for the reasons to be discussed, i.e. a rare and not yet identified mutation (see the discussion on the family, section 5.3). This may give a false sense of well-being to the individuals. Second, information of having had a genetic test performed in the past, may have to be shared with other third parties, like insurance companies when applying for insurance or healthcare cover. This will also affect other family members, as the application and health questionnaire may enquire whether any other family members had undergone genetic testing in the past, which may potentially be used to exclude certain conditions from the benefits or may result in higher premiums.

Due to the development of more sophisticated and readily available genetic techniques, hereditary cancer syndrome is becoming a growing group of diseases. This thesis specifically addresses one important aspect of the management of these diseases, i.e. who is the owner and guardian of the generated genetic information.

3 Our changing perspective of medicine and genetics

3.1 The concepts of health and disease

The medical profession is often regarded as the oldest profession in the world. However, between the practice of medicine of the past and antiquity and the medicine of the present is an abyss filled with different concepts and understanding of health and disease. The lack of knowledge of basic anatomy, physiology and pathology concepts in the past led to the mystification of disease and illness, and this often created the hieratic and theocratic beliefs on the causes (and cures) of diseases (Rooney 2009, Orfanos 2007, Jonsen 1990).

Human disease was originally seen as a supernatural event or as punishment for sins and living an unpure life in the eyes of the gods or not keeping to the prescribed rituals. It was also sometimes perceived to be an invasion by an evil spirit. The healing process was therefore managed by priests in theocratic societies, or by witchdoctors, sorcerers or shamans in other primitive cultures.

During the 10th and 9th centuries BC, the ancient Greeks conceived the concept of health, especially as seen from a Western perspective (Rooney 2009, Orfanos 2007, Jonsen 1990). This was deified in the goddess Hygieia, the daughter of the demigod Asklepios, son of Apollo and Koronis, a human female. Asklepios played a central role in ancient medicine. Hippocrates called the site where he practised medicine on the island Kos, Asklepieion, to recognise the role of the demigod in healing. The Hippocratic Oath also refers to the deities Apollo, Asklepios and Hygieia and medicine's symbol still honours the role of Asklepios's snake in healing the sick by a touch of the tongue. Finally, it appears as if Asklepios was most probably a victim of being "too competent", as he was killed by Zeus while trying to save a man whose life was already condemned by the gods (Jonsen 1990, p.20). This scenario is still very relevant today. The issue of being "too competent" is a moral issue encountered more and more in modern medicine with our advanced life-supporting systems. In medicine there is a point where the clinician must allow nature to proceed on its own, or in the words of Hippocrates himself, as quoted in Jonsen (2006, p.670), "and not to attempt to cure those who are mastered by their disease".

According to Hippocrates (460 – 375 BC) (Rooney 2009, p.18) the concept of "physis", or of "disease", was viewed "as a kind of physical dysfunction or disorder that leads to lack of mental and somatic completeness and strength and therefore makes life uncomfortable" (Orfanos 2007, p.852). He created the humoral theory, based on this belief and also taking into account the concept of nature as defined by the early Greek philosophers, like Thales, Pythagaros and Empedocles, as consisting of air, earth, water and fire, as well as Alcmaeon's concept of elemental pairs of opposites. According to this theory, the four humours consisted of black bile, yellow bile, blood and phlegm, and had to be kept in balance to maintain good health. This was the dominant model of medicine in Europe and the Middle East from the 5th until the 19th century (Rooney 2009).

Aristotle (384 – 322 BC) (Law 2007, p.248), who was born seven years before the death of Hippocrates (460 – 375 BC), also supported this theory. His interpretation of the Hippocratic texts, i.e. that "every symptom implied its own form of illness" contributed to his conceptualisation of logic (Strathern 2005, p.15). The humoral theory was further developed by the Greco-Roman doctor Galen (129 – c.216 AD) and by the Arab doctor Avicenna in the 11th century. At its peak it did not only try to explain diseases, but also the temperaments of individuals; for instance, someone who has too much blood will be courageous, hopeful and amorous, while too much yellow bile will cause bad-temper and to be quick to anger (Rooney 2009, p.17).

Hildegard of Bingen (b.1098) ingeniously succeeded in linking the humoral theory to religion (Strathern 2005, p.47).

> ….the unbalanced nature of the four humours resulted from the fall of man in the Garden of Eden. After Adam ate the apple (the fruit of the knowledge of good and evil), its juices entered his blood and disturbed the humoral balance of his body. As a result, his blood was able to produce the poison of semen. This substance resulted from the foaming of the blood. In women, the same process resulted in the production of breastmilk.

For her, sins resulted in an unbalanced state of the humours, and thereby caused disease. During the Middle Ages, when diseases like plaque (Black Death) killed one quarter of

Europe's population between 1347 and 1350, some Christians attributed disease to the punishment and wrath of God. The story of the Biblical figure, Job, however did not support this argument; how could a righteous man such as him be afflicted by pestilence and disease (including even the possibility of having suffered from syphilis) (Cruse 1999) (Strathern 2005, p.84).

At the same time, most of the Eastern medical systems also promoted the importance of a system of balance as a requisite for health (Rooney 2009, p.13). These included *Ayurveda* in India, the oldest surviving and continuing medical system, where a holistic approach to treat the body, mind and spirit together, was aimed at balancing the three *doshas* (wind/spirit/air, bile and phlegm) in the body. The Chinese system of *yin* and *yang* and the Buddhist and Hindu belief systems of *chakras,* or energy centres, are all based on the principle of balance as a requirement for health.

Although Hippocrates did implement different medical terminology terms still in use today, like erythema for redness and alopecia for hair loss, he regarded illness or disease as one entity. In the Hippocratic tradition, disease, and the way it manifested itself, was "entwined with the life history of the patient suffering from it" (Van Niekerk 2002, p.228). The aim of medicine was thus to cure the sick by correcting the imbalances in the body in a holistic manner.

It was only during the latter part of the previous millennium that a scientific approach to medicine, built on anatomy, physiology, pathology and pharmacology, developed. The proliferation of knowledge was the result of many factors, including a more liberal religious position on the dissection of corpses, the development of the printing press to disseminate knowledge and the development of the microscope. By identifying different causes for different diseases, it became not only possible to treat the sick, but also to prevent the development or spread of diseases. Thomas Sydenham was instrumental in the development of the science of pathology in which disease is not regarded as a uniform condition, but as different entities, caused by different agents and therefore requiring unique and specific treatments (Van Niekerk 2002, p.227).

Henry Sigerist (as cited in Jonsen 1990, p.84) explains this difference between Hippocratic medicine and the modern understanding of medicine as formulated by Sydenham, as follows:

> Hippocrates recognized only disease, not diseases. He knew only sick individuals, only cases of illness. The patient and his malady were for him inseparably connected as a unique happening, one which would never recur. But what Sydenham saw above all in the patient …. was the typical, the pathological process which he had observed in others before and expected to see in others again. In every patient there appeared a specific kind of illness. For him, maladies were entities, and his outlook upon illness was, therefore, ontological. Hippocrates wrote the histories of sick persons, but Sydenham wrote the histories of diseases.

A natural consequence of this scientific approach to medicine was the definition and formulation of a disease according to its etiology, pathophysiology, morphology, clinical manifestation, management, pharmacological therapy, and also prognosis. Genetic predispositions or abnormalities, as one of the causes for diseases and ailments, became more and more important as we started to understand this “unseen or invincible” science at play.

3.2 The concepts of inheritance and genetics

Since ancient times, the human race has been aware of the importance of inheritance, and especially the fact that some hereditary traits may be inferior or superior to others. The ancestral line of origin was also often central to the succession of power, and most Old Testament books deal extensively with the genealogy or family lineage of important Biblical characters.

It was also in these ancient times that humans started the process of not only domesticating animals and crops, but also aiming to improve the quality of the produce. The first reference to the application of biotechnical manipulation is recorded in the book of Genesis, chapter 30. This tells us how Jacob created a flock of superior goats by using the basic principles of

genetic selection and crossbreeding, much to the dismay of Laban, his father-in-law, as well as his brothers-in-law (Kegley 1998, p.72).

Philosophers and physicians in Greco-Roman times also reflected on the concepts of inheritance. According to Retief and Cilliers (2001) the so-called Pre-Socratic Greek philosophers, like Anaximander, Alcmaeon, Hippo, Empedocles, Diogenes and Democritus, all formulated different theories during the sixth and fifth centuries BC. These philosophers postulated that the transfer of hereditary characteristics is the result of male and female semen or seed (or the female equivalent of semen). Opinion on where and how semen was produced in the body often differed and gave rise to a number of theories. These included the production of semen in the brain during coitus (the encephalogenic theory), passing along the spinal cord to the genitals (the encephalo-myelogenic theory) or absorbing all the characteristics of the organs and tissues as it passes through the body (the pangenesis theory).

During the era of Hippocrates during the fifth and fourth centuries BC, physicians developed a complex hereditary theory, based on the humoral theory. They believed that both males and females produced seed, but other factors would determine the offspring's characteristics (Retief & Cilliers 2001, p.96). These included the quantity and strength of the semen, the origin of semen (left or right side of the body), the site of uterine implantation, as well as the temperature and moistness of the parents' bodies.

Aristotle (4th century BC) promulgated a thesis based on the superiority of the male (*op. cit.*). According to him only the male produced semen and menstrual blood merely serves as a substance to facilitate growth of the embryo and fetus. Although all children should ideally be born males resembling their fathers, other factors may influence the developing embryo to result in a spectrum of male-female offsprings with at the two opposing poles a male or female. These influences included the age of the parents, weather conditions, the type of water drunk, the viscosity of semen, etc. He rejected the pangenesis theory and stated that semen originated from the froth in the blood, produced by heat during coitus (the haematogenous theory).

For centuries, the concept that the reproductive processes was dominated by the male, who was by implication therefore responsible for most or even all of the hereditary traits of his descendants, was the accepted theory of procreation.

3.3 The Mendelian gene and the molecular gene

It was only when Gregory Mendel demonstrated the equal role and contribution of both parents to the creation of a gene pool with equal amounts of maternal and paternal genetic material, that the modern view on inheritance was established (Griffiths and Stotz 2013, p.10). Mendel, a Catholic monk and scientist, experimented on peas of different colours and heights. The concept of the Mendelian gene is based on different alleles at a specific locus on the chromosome, and the dominant or recessive nature of the allele will determine whether it will be expressed or not, depending also on whether it is homozygous or heterozygous[9].

For a long period of time, however, genetic analysis had to be performed mostly indirectly and by way of inference, as the analysis of genetic material was limited to observations at the chromosomal level.

The Watson and Crick model of the DNA structure was the first step in understanding the building blocks of the encoded genetic information. As newer techniques developed, it became possible to sequence the genome and the genes associated with abnormalities in the human phenotype.

The molecular gene is defined by the nucleotide sequence of a particular gene. Base pair changes, like deletions and insertions, in the nucleotide sequence may result in mutations. A specific genetic abnormality as identified by Mendelian genetics may be the result of different molecular genetic (and epigenetic) influences.

[9] Zygosity refers to the degree of similarity between the different alleles for a specific trait at a particular locus on a set of homologous chromosomes. Alleles are homozygous if they are identical and express the same trait. In the situation where both the alleles are recessive, the recessive trait will be expressed. If the alleles are heterozygous for a specific trait, only the dominant trait will be expressed

Griffiths and Stotz (2013, p.61) support this dual approach, recognising the importance of both the Mendelian and molecular gene:

> Instead, in one experimental context, that of hunting for the mutation responsible for the phenotype, the gene takes on its Mendelian identity, while in the other context, that of analysing the sequence, the gene takes on its molecular identity.
>
> So one clear sense in which Mendelian genetics does not reduce to molecular genetics is that it is not superseded by molecular genetics, but remains alongside it as another way of thinking about DNA. Molecular genetics did not reduce or replace Mendelian genetics, but enriched genetics with another way of think about genes: as Mendelian alleles and as sequences that template for a product.

4 Phenotype and genotype: a justifiable distinction?

4.1 Introduction

For many years, we viewed the phenotype and genotype of an individual as two completely separate concepts. These two concepts are defined by Richard Lewontin (2011, p.1) respectively as follows:

> The genotype is the descriptor of the *genome* which is the set of physical DNA molecules inherited from the organism's parents. The phenotype is the descriptor of the *phenome*, the manifest physical properties of the organism, its physiology, morphology and behaviour.

As will be discussed in more detail below, I believe that the boundaries of these two concepts have blurred to such an extent, that in fact, I would like to argue that they have merged and therefore need to be seen as different reflections of the same entity. Such a model has ethical implications in the way we practise medicine, and especially when dealing with the histopathology examination of a tumour. If we accept a unified concept with the phenotype and genotype only representing two reference points on a spectrum of expression of the human body, then we need to adapt our consent procedures and protocols to reflect this view, especially when dealing with the diagnosis and analysis of a tumour.

I will discuss the present practice, or rather the lack thereof, regarding obtaining consent for the examination of histopathology specimens, and address the benefits of a unified approach. After a short review of the history of the concepts of genotype and phenotype, the argument that these two concepts have merged will be supported by a discussion on how techniques like immunohistochemistry and gene expression profiling have influenced histopathology analysis. This will be followed by a discussion of the consequences of such a merged and unified concept, and the implications this will have on the future duty of the modern histopathologist.

4.1.1 Consent procedure for pathology investigations

Tissue specimens for histopathology examination are obtained during a surgical procedure. It is unfortunately common practice that the whole procedure to obtain consent for a surgical intervention or operation will focus primarily, and often exclusively, on the surgical aspects. These will include the type of anaesthetic procedure, the surgery and the consequences thereof, like the loss of an organ, and any possible complications. Any reference to the histopathology investigation is usually limited to a passing remark that the tissue will be sent to the laboratory for a pathologist to decide whether it is a benign or malignant lesion. No specific consent for the histopathology examination of the tissue is obtained.

The above lack of consent for histopathology investigations is not unique, and is also seen in other pathology investigations, like haematology, biochemistry, etc. The demographic information required on the pathology request forms in use in South Africa usually have two different sections; one to be signed by the patient to consent to the investigation, and a section for the guarantor, if not the patient, accepting responsibility for payment of the laboratory investigations. The latter is also a legal requirement of the Consumer Protection Act (2008). Most pathology request forms, however, are returned unsigned to the pathology laboratory. In the hospital environment specifically, patients are either unconscious or critically ill when the specimen is collected, or only give implied consent by allowing the phlebotomist to collect the specimen. These aspects are of concern to pathology groups, as it carries both professional and legal risks.

It is important that any interaction with the patient when obtaining consent for any surgical procedure, must be used as optimal and productive as possible. The consent obtained must be comprehensive enough to include any further testing of a specimen if deemed necessary. In practice, the clinician needs to inform the patient not only about the surgical procedure, but also that the specimen will be submitted for histopathology examination, and that, depending on the findings of the pathologist, further tests and analyses may be performed on the specimen, which may include genetic testing. Consent is an integral aspect of the respect for persons and their autonomy. It is therefore important that patients are allowed to make an informed decision on how the investigation and diagnostic work-up of their

tissue specimen will proceed, otherwise the pathologist may be blamed for acting paternalistic and even without the necessary consent.

The alternative is to follow a more cumbersome and staggered approach, dictated by the type of tumour and its known potential genetic associations. First, only the morphological diagnosis of the tumour is performed with the implied consent of the patient, as this is the situation we usually found ourselves in at present. If the pathologist believes that the tumour may harbour somatic mutations, which may be of therapeutic/prognostic significance, informed consent for the performance of genetic testing to determine the presence or absence of these mutations needs to be obtained. Finally, if the pathologist identifies certain morphological features, which may indicate a hereditary cancer risk, additional informed consent for the performance of genetic studies to determine the presence of germline mutations has to be obtained. In practice, this approach is not only difficult and time consuming, but it also delays the final diagnoses, as the patient will have to be counselled at successive consultations as the histopathologist unravels the characteristics of a particular tumour.

By merging the concepts of phenotype and genotype into one entity, consent obtain for the examination of the tissue specimen will be comprehensive and inclusive of both histopathology as well as any genetic studies, which may be deemed necessary. In other words, a proper consent procedure addressing all the aspects related to the examination of a tissue specimen will cover all the above aspects and procedures in advance and with the patient's express consent and permission.

4.2 Historical background to the concepts of genotype and phenotype

The realisation that the hereditary and developmental characteristics of organisms differ, formed the basis on which Wilhelm Johannsen introduced the distinction between genotype and phenotype in 1908. He used an appearance-type (*Erscheinungtypus*) approach in his definition, stating that "the phenotype of an individual is thus the sum total of all his

expressed characters" (Johannnsen 1909, p.163, as cited in Nachtomy *et. al*. 2007, p.240). The definition of these two concepts by Richard Lewontin has already been mentioned, but it is important to emphasise his comprehensive definition of the *phenome*, as it not only limited to the physical properties of an individual, but it also comprises the intangible characteristics of the individual, i.e. its physiology and behaviour (Lewontin 2011, p.1).

Two informational processing systems determine the ultimate phenotype expressed by an organism (Strohman 1987). The one is the genetic system where linear genetic rules govern the flow of information from DNA to RNA[10], and ultimately proteins. At the same time, the epigenetic system allows for an interactive network with environmental signals, which then regulate the genome via a feedback loop and alter the patterns of gene expression. This latter pathway explains why no two individuals, including genetically identical twins or even cloned organisms, will be an exact copy with the same phenotype, whether physical, functional or behavioural.

In the Mendelian era, this simplistic relationship between the genome and the phenome was acceptable. However, genetic and molecular studies have shown that our genome is not immune to external factors, which will also be expressed in our phenotype. Radiation, and its effect on both somatic and germ cells, is a well-known example. Most, if not all, tumours result from genetic information and control going haywire. Scientific developments in molecular pathology and histopathology are constantly changing our view of tumours; it is no longer only a cluster of malignant cells, but it has indeed been reduced into an encoded genetic event with consequences.

4.3 Reductionism in medicine

It is often said that the genetic code in living beings and medicine can almost be compared to the role of the atom in physics. Genetic determinism, or the term genetic essentialism as

[10] Ribonucleic acid (RNA) is a single-stranded molecule involved in various biological processes like coding and decoding of genetic information, regulation, and expression of genes. Different types of RNA exist, including messenger RNA (mRNA), transfer RNA (tRNA) and ribosomal RNA (rRNA).

used by Kegley (1998, p.48), is a form of reductionism and "the aim of reductionism is to show that one level of reality …. can be explained by a lower and 'deeper' level of reality".

Genetic determinism and reductionism carry the risk that it elevates the concept of the genotype to a sacrosanct position, ignoring the important role of external factors in defining the phenotype. The genotype, and the owner of the body in which it resides, is then believed to have the ultimate and final say and becomes the de facto gatekeeper of the scientific information locked up in the individual's genetic code.

There had been a change in our understanding of the concept of genetic determinism (Chadwick, et. al. 2014, p. 14). The original model was built on a "gene for x" approach, but the Human Genome Project identified far less genes that had been expected (20 500 versus 100 000). As it was obvious that such a small number of genes could not solely be responsible for the complexity and diversity of the human species, it was argued that other factors must also play a role. The debate was therefore about "the difference between the ways in which a gene can influence rather than determine" (*ibid*., p.15). Even so, the Human Genome Project is still of tremendous assistance in our understanding of the genetics of tumours, partly because it enables us to define the concept of the "normal", or wild-type[11], gene pool

The emerging view of genetic determinism, which differs from the above "gene for X" concept, is the idea "that the genome in all its complexity is deterministic, taking into account the volume of data that can be made available of the precise sequence in an individual's genome, including all the myriad ways in which he or she differs from other individuals" (*ibid.,* p.15)(my emphasis). This includes the influence of epigenetic factors, like DNA methylation, histone modification, non-coding RNA (nc-RNA) and cytoplasmic inheritance on the expression of information encoded in the genetic sequence, the latter also called Crick information (Griffiths and Stotz 2013, p.109).

The concept of genetic determinism appears to be more controversial in the field of behavioural genetics, where an attempt is often made to reduce human behaviour, including gender and sexuality, to a genetic base. In reality, only a few conditions can be

[11] The normal or non-mutated genetic sequence or gene is also known as the wild-type gene.

reduced to a single genetic abnormality. These are limited to the few truly monogenetic conditions, like Duchenne muscular dystrophy and haemophilia. Most other conditions, like hereditary cancer syndromes, are polygenetic and/or multifactorial in nature with epigenetic factors also playing an important role.

There appears to be more sensitivity and respect for the information encoded in the genetic make-up of an individual, than for his physical and other tangible characteristics, like behaviour and intellect. As already stated, the genotype is regarded as almost being sacrosanct, while the phenotype is open to public scrutiny, criticism and even sometimes ridicule. Is this genetic essentialism based on the argument that one cannot alter your genes, but that your physical, behavioural and other properties are to some extent the product of external factors and influences and may be modulated?

We need to have a less strict definition of what is regarded as genetic determinism and genocentrism, and recognise the role of all other factors, like epigenetics and the environment, at play together with the genetic sequence in influencing, rather than determining, the phenotype. Such an approach is in line with my argument that we tend to be "over-protective" of information related to our genotype; in reality, our genetic material is only one part of our identity – physical, behavioural, emotional and intellectual. In mathematical terms, the equation genotype = phenotype has rather changed into an approximation with genotype ≈ phenotype.

4.4 Immunohistochemical definition of the phenotype

The concept of medicine, and in particular our understanding of disease, has evolved through centuries into a scientific and evidence-based discipline. This was discussed in more detail in chapter 3. Even as a scientific-based profession, our understanding of pathology was for centuries limited to what we could see; at first only with the naked eye (macroscopy), but since the second half of the nineteen century also on a microscopic level. During the last couple of years, other techniques have developed which enable us to view cells in both a morphological and functional perspective. Firstly, we developed the ability to analyse the production and expression of proteins (receptors, enzymes, etc.) using

immunohistochemical stains (see p.15). Secondly, techniques like gene expression profiling, allow us to determine which genes are activated in a particular cell (Coleman and Tsongalis 2009; Turnpenny and Ellard 2012).

The impact of immunohistochemistry as a morphological reflection of the genetic information encoded in a tumour cell, can best be illustrated using two practical examples.

Breast cancer is still the most common cancer amongst women in developed countries. We are able to determine the presence (qualitative and quantitative) of estrogen receptors in the breast cancer cell. This identifies the subgroup of breast cancers in which we can treat the patient with anti-estrogenic drugs, in an attempt to block these receptors and to inhibit tumour growth. Any clinician views this information as a vital and integral component of the histopathology report, and these tests are routinely performed without any specific consent obtained from the patient, other than the routine express consent for the operation and (usually) only the implied consent for the histopathology examination of the specimen. Although it reflects unique characteristics influence by the genetic profile of that particular tumour cell, it raises no ethical issues regarding the way that information must be treated as it only reflects a somatic cell change. It does not reflect any germline or familial genetic trait.

What is the situation in the diagnosis of Lynch syndrome where we can identify those individuals who may harbour a germline mutation, by using immunohistochemical staining techniques? Albeit not a diagnostic or confirmatory test and genetic confirmation is still required, it places the individual in a high-risk group. Can these tests be performed without obtaining specific consent? Lynch syndrome is a fitting example of the blurring of the borders between the concepts of phenotype and genotype. In Lynch syndrome, one of the morphological presentations, although not specific for the condition, is the loss of mismatch repair (MMR) proteins. These proteins, or the lack thereof, can be demonstrated with immunohistochemistry stains. It may be argued that proteins are more on the phenotypic rather than the genotypic side of the fence, as they can be regarded as the building blocks for the cell and organism. However, they are the direct products of the genetic controlled amino-acid assembly system, and abnormal amino-acid sequences will result in abnormal proteins or the loss thereof.

The historic definition of the genotype and phenotype is only separated by one single step, i.e. the translation of the genetic sequence into the amino-acid sequence. It is merely a reflection of the same image in a mirror (genetic sequence *versus* amino-acid sequence) and reflects the collapse of the genotype-phenotype spectrum into one unified concept.

When dealing with a possible case of Lynch syndrome the pathologist will be guided by an algorithm (see annexure A, p.106). In the work-up of the case, there is a transition from the morphological findings, like immunohistochemistry, to the genetic features. The exact point where this transition into the realms of genetic information occurs, is not properly defined. This is reflected by the fact that there are two schools of thought regarding the performance of immunohistochemistry to confirm/exclude mismatch repair protein loss. The majority of histopathologists regard immunohistochemistry as part of the work-up of the patient as a screening procedure based on the morphology of the tumour. As it is not a diagnostic tool for Lynch syndrome, they believe that it is permissible to be performed under the (non-genetic) consent obtained for the surgery. However, there is a school who believe that immunohistochemistry, even though it is only a screening procedure, cannot be performed without the express consent of the patient (Kalloger *et al*., 2012). These two schools reflect the difference in understanding of the phenotype/genotype concept amongst histopathologists.

4.5 Gene expression profiling defining the genotype or the phenotype?

What about other techniques straddling the genotype-phenotype fence? Although gene sequencing has become common practice in medicine, both as a research and diagnostic tool, other techniques have also been developed to measure the activity and expression of genes by measuring and profiling the messenger RNA or mRNA in the cells.

Along the genotype-phenotype spectrum, RNA, and specifically messenger RNA (mRNA), can be regarded as the interface between the genetic information encoded in the DNA of the genome in the nucleus, and amino acids, polypeptides or proteins as structural building

blocks in the cellular cytoplasm. It is at this interface where genetic information is translated into structure. It is now possible to determine the extent to which the genetic information encoded in the genome of a particular cell is expressed by analysing and measuring the expression of mRNA by a cell. This is called gene expressing profiling, and is done by microarray-based hybridisation assays. Like most laboratory techniques, the commercialisation of the newer generations of these tests has moved it from a research tool into general practice.

Although all non-neoplastic somatic cells in an organism will for all practical purposes have the same identical DNA sequence, each different type of cell will have a unique expressed genetic profile, as its cell type and function will determine which proteins are required and therefore need to be produced by that particular cell type. The expressed genetic profile of the organism as a whole will therefore be the sum total of all the different profiles expressed by all the different cell types, and this may vary from time to time depending on the stage of development or the metabolism of the organism.

Gene expressing profiling has for instance demonstrated that there are different types of breast ductal carcinoma. Morphologically these carcinomas may look the same, but they do not only arise from different cell types of the breast duct, but also show a difference in response to therapy and prognosis. Commercialised systems to predict prognosis and the need for adjuvant therapy, like Mammaprint® and OncotypeDX®, are already widely available, although its use in South African practice is still limited by cost factors. The point of interest is that no specific “genetic” consent is usually required for the performance of these tests.

4.6 The consequences of the merging of the concepts of genotype and phenotype

What are the practical implications in modern medicine, and in particular biomedical ethics, if the merging of the concepts of genotype and phenotype as a continuum of expression, is accepted? Such a unified concept will “defragment” the analysis of tissue specimens, and

will enable the pathologist or medical practitioner to obtain the maximum scientific information from the submitted specimen.

When a surgical specimen is submitted for histopathology examination, good clinical practice requires that the pathologist will issue a comprehensive report which will include specific reference to: 1) the morphological diagnosis, including the tumour grade and prognostic features, like lymphovascular involvement; 2) adequacy of resection with specific reference to the surgical excision margins; 3) an indication of whether pharmacogenomic modalities may be of value in the treatment of the patient (like estrogen receptor or *Her-2* status in the case of breast cancer) and 4) comment on the possibility that the tumour may be the result of an inherited genetic abnormality. It is especially in these last two very important aspects, where the distinction between genotype and phenotype becomes difficult to justify.

As stated above, it is standard practice to accept that the consent obtained for the operation and subsequent histopathology examination, albeit that the latter consent is usually implied and not necessarily express, will only include any genetic studies to determine response to therapy (pharmacogenomics) as well as prognosis. This is called "somatic genetic profiling" (Robson *et. al*. 2010, p.893). Germline testing for the inherited predisposition of cancer falls at present outside the scope of the consent obtained for the surgery and examination of a tumour. Even though the pathologist may have a high index of suspicion that the cancer may be due to a hereditary genetic disease, genetic testing to establish such an abnormality cannot proceed unless specific consent to that effect is obtained. I believe that this approach does not always serve the best interest of the patient, in particular as the clinician may inadvertently omit to inform the patient of this possible risk, especially in practice as the patient is usually referred by the surgeon to the oncologist for further management at this stage. It is known that in the fragmented world of super-specialised medicine, important information can inadvertently be lost in the communication amongst all the different role-players.

4.7 The duty of the histopathologist

If a tumour is submitted for histopathology examination, it is the responsibility of the pathologist to generate as much possible scientific information from that specimen, including whether the tumour is the result of a hereditary genetic effect. This forms an integral part of the information conveyed to the clinician, which will form the basis of the further management of the patient. The primary aim is to benefit the patient. Not recognising the possibility that you may be dealing with a genetic syndrome, or not excluding such a possibility if it does feature in the assessment of the specimen, may put the patient at unnecessary risk for the development of other synchronous or metachronous tumours. At the same time, it may prevent at-risk family members from seeking genetic guidance and institute preventative measures.

Not providing optimal care to the patient may amount to negligence. According to Beauchamp and Childress the professional model of due care, and therefore the criteria to assess negligence and medical malpractice, consists of the following elements (Beauchamp and Childress 2013, p.155):

1. The professional must have a duty to the affected party.
2. The professional must breach that duty.
3. The affected party must experience a harm.
4. The harm must be caused by the breach of duty.

Although the histopathologist may not enjoy the same personal and intimate relationship with the patient as his clinical colleague, and may remain for all purposes anonymous to the patient, he nevertheless has a similar professional duty. The patient has the right to expect that the professional duty of a histopathologist includes the assimilation of all relevant information related to a tumour. Failing to do so may result in harm and can be regarded as being professionally negligent.

Identifying a genetic basis for a tumour is not necessarily only gloom and doom, as it may also harbour some good news for the patient. It is known that the prognosis of some tumours caused by a genetic syndrome is better than those tumours arising *de novo*.

It is therefore important that medical practitioners change the way consent is obtained when dealing with a possible malignant tumour. This consent must include consent for the performance for a complete, all-inclusive and comprehensive analysis of the specimen, including any genetic analysis deemed necessary by the pathologist.[12] The final histopathology report on the specimen must therefore include the criteria as set out above, and in addition comment on the absence or presence of a hereditary cancer syndrome.

It is important to note that we have so far only been dealing with the genetic information pertaining to the index patient or proband[13]. The further dissemination of the genetic information amongst family members, and in particular the issues of consent, confidentiality and privacy, will be discussed in more detail in the sections below.

[12] Although it is technically possible to perform any type of genetic testing on a tissue specimen, a blood specimen is preferred in practice due to the better preservation of DNA and RNA.

[13] The index patient or proband is regarded as the first member of a family to have been identified as being at risk or affected.

5 Third parties and their interest in an individual's genetic information

The ownership of genetic information is central to the debate if, and to what extent, any individual can control the dissemination of information regarding his or her genetic profile especially if that information may identify potential hereditary genetic risks for other family members. We share so much genetic information, not only amongst ourselves as human beings, but even with other species, like primates. This places an individual in a central position in as far as the flow of genetic information is concerned; not only will he be able to analyse his own genetic profile, but this will also reflect information inherent to his family and even his society. It can therefore not be a matter of sole ownership; it must be regarded as information in the public domain as it is a reflection of the genetic information of humankind, society, family and ultimately the individual.

5.1 Humankind

Humans share a large amount of genetic material. The Human Genome Project (National Human Genome Research Institute, n.d.) did not only quantify the genetic information, but also succeeded to identify some of the genetic differences amongst humans. The human genome consists of approximately 20 500 genes, of which 99% are common to all humans. The remaining 1% of our genome results in individual diversity through polymorphism, the difference in genetic material, which makes people different and unique. Although our phenotypes may be vastly different, our genotype shares a vast amount of genetic information. Are we as individuals the gatekeepers to our common genetic heritage and information, or does it belongs to *Homo sapiens* as species?

By using the normal or wild-type DNA sequences as the norm or reference, we are able to identify abnormal genetic sequences and mutations as well as their association with disease, including cancers. This genetic information may be regarded as the equivalent of "open source" information technology; it resides in the public domain and is available for the benefit of the public at large.

An argument can therefore be made for the unrestricted bidirectional flow of genetic information to benefit all humans. In other words, if an individual suffers from a genetic disease and analysis of his genetic profile results in the identification of a specific genetic abnormality and mutational sequence, can he decline the dissemination of that information into the public domain? I believe not, especially as that information can be anonymised with no risk of invading his privacy. Whether he must be allowed to benefit materially for "supplying" that information, is another debate. Obviously, he stands to benefit just as much from additional information contributed by other patients to our understanding of disease. Our current understanding of the human genome and the information derived from it must remain readily available to the benefit of all humans.

This raises another, and almost similar, issue. Patent rights are quite common in the medical industry, especially in pharmacology and in medical technology. Patent rights are also often regarded as one of the major cost drivers in healthcare. Nevertheless, at present this is one of the only ways how pharmaceutical companies and other research facilities can recoup their investment in research.

However, can genetic information, and in particular that of the human genome, be patented? I believe that patent rights on natural occurring DNA sequences and other genetic information, even if it fulfils the legal requirements of a patent, cannot be ethically and morally justified. The Nuffield Council of Bioethics (2002) in its discussion paper on the patenting of DNA, highlighted the special status of our DNA. This special status is supported by different concepts like our genes as common heritage, the inalienable nature of our genes as well as our genes as public property. The importance of the common heritage concept in the argument against patenting of the human genome or portions thereof, is also emphasised by Ossorio (2007). This view is also supported by Holtug (2012), stating "patents that would interfere with human autonomy or freedom would be quite dubious according to almost any moral view, whether they were issued on human genes, organs, or even on entire human beings." He does not specify to whom specifically the concepts of autonomy or freedom apply, i.e. the individual harbouring the genetic abnormality ("owner") or society who stands to benefit from the use thereof ("user"). For the latter group, restricted access governed by patent rights does limit someone's freedom to obtain information, and the lack of that information may affect the quality of any decision-making

process and therefore the autonomy of the individual. Patenting our common heritage or parts thereof will deny others unrestricted access to their own genetic material.

It also raises the question of ownership of patents on unique genetic sequences. Who has the right to patent it? The individual harbouring the sequence, or the institution performing the sequencing and identifying its significance? Can you patent part of someone else's body and can an individual sell (even minute) bits of his body?

The ownership of biological material has and will always be a contentious issue. Although any individual has a body, and by living through by means of that body, can also state he or she is a body, the concepts of "I have a body and I am a body" have limitations. I cannot sell my body parts which are not renewed or replaced by the normal natural processes of life. That is not only against the law, but also *contra bones mores*, against the morals of society. Even remuneration for donating blood, a renewable body product, raises the ethical dilemma whether this would not attract donors, which are usually regarded as unfit for blood donations, like drug abusers. Adding a monetary value to a human product creates the potential for actions driven by greed and not altruism, allowing a drug addict for instance to "sell off" bits and pieces of their body to fund their habits. The same applies to tissue processed in the routine as well as experimental medical settings; if a specific gene is identified, its individual genetic footprint is just part of the spectrum of genetic sequences or expressions determining health and disease, and not necessarily an event unique to that individual. The human genome has only so many ways (or sequences) to dictate health and disease.

The ownership of genetic information, and in particular the validity of gene patents, was central in the recent American court case between the Association for Molecular Pathology and Myriad Genetics (Association for Molecular Pathology v. Myriad Genetics 2014). At issue was the patenting of the BRCA1 and BRCA2 genetic sequences. These genetic sequences are used to diagnose individuals with a hereditary risk for *inter alia* breast and ovarian cancers. It has been widely used in clinical medicine throughout the world since 1996. Initially there have been conflicting rulings in the District Court and the Court of Appeals for the Federal Circuit, the former ruling it "not patentable" and the higher court subsequently overturning that ruling.

In June 2013 the Supreme Court of the United States ruled that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA[14] is patent eligible because it is not naturally occurring" (Association for Molecular Pathology vs Myriad Genetics 2013, p.1). This ruling is in line with my argument that most, if not all, genetic sequences, whether abnormal or normal, are common to all human beings and products of nature. It cannot be patented. However, any scientific technique or method to demonstrate these abnormal sequences and mutations, like the use of complimentary DNA as probes, can be patented.

This important ruling therefore supports the special status of our naturally occurring DNA (and by inference our genome); although scientific techniques and methodologies may be patented, the genetic information must remain in the public domain.

5.2 Society

Man and his family do not live in isolation, but are part of a society, defined by culture, race, geography, etc. Societies often tend to share the same genetic pool. Often this sharing of genetic information is further accentuated by marriages between people of the same society. This undiluted gene pool created by inbreeding carries a risk for increased genetic abnormalities, including polygenetic and multifactorial diseases like hypercholesterolemia. These diseases are often well researched, sometime to the extent that the founder families who introduced the mutation can be identified. For instance, researchers at the University of Stellenbosch have recently identified a common founder couple, who came to the Cape in the 1650's, for Parkinson's disease amongst the Afrikaners in South Africa (Geldenhuys *et. al.* 2014).

In some cases, details of the genetic information of a particular society may have a profound effect on their culture and their beliefs. This was the case with the Havasupia tribe of the Grand Canyon in the United States, where researchers of the University of Arizona conducted migration studies, without the necessary consent, on samples previously

[14] Complimentary DNA.

obtained for the study of medical conditions, like type II diabetes (American Indian and Alaska Natives Genetic Resource Centre, n.d.). These findings showed that their origin was not according to their belief and folklore of being placed by a big bird in the canyon and tasked to guard it, but rather that they migrated from Eurasia across the Bering Strait. They successfully sued the University of Arizona, for what was regarded as genetic piracy.

Southern Africa, as the cradle of humankind, is a rich source of genetic information regarding the most primitive tribes and subsequent population migration. In the South African context, migration and population studies may even have an important socio-political role to play, as these studies may be able to establish the rightful owners in land dispute claims.

Who is the owner of this societal genetic information? The individual or the society? We know that certain societies may have unique genetic abnormalities. For instance, different genetic abnormalities exist in the BRCA1 gene, some of which are based on origin (including Afrikaner, Ashkenazi Jew, etc.). Knowledge of someone's origin improves the changes of identifying a specific genetic mutation common to that particular society.

Just as the genetic information encoded in the human genome belongs to humankind, the same principle of genetic information belonging to the public domain, applies to a society. However, societies have to be involved in influencing genetic research. Consent by a community or society is important, especially if information obtained from genetic research my affect their beliefs and culture.

5.3 Family

Shickle (1998) raises the question how the family unit must be defined. Should the definition of the genetic family only be limited to the nuclear family, and if not, how shall the boundaries of the extended family be defined? If only blood relatives are members of the genetic family, what about the interests of relatives by marriage, like the spouse of the patient? Although not genetically linked, these individuals may have to carry not only the financial and emotional burden of the disease, but may also have to care for at-risk

individuals, like children. Do they have any say in the dissemination of genetic information, especially after the death of the index patient? For instance, do they have the right to block the dissemination of such information to other members of the index patient's genetic family?

Parker (2012) makes a distinction between the different concepts of the family as represented in the family tree or pedigree: the "family as biology", the "family as culture" and the "family as part of multiple families". Amongst this, the "patient in the families" is to be found.

The family as biology and the family as culture do overlap, but are not necessarily identical. The family as biology represents those individuals sharing the same pool of genetic information and they are all genetically linked, either vertically or horizontally. The family as culture also includes those members who are not genetically linked, like spouses. Numerous factors, like separation of family members, divorce and adoption may disrupt the cultural family, although the genetic linkage and therefore the family as biology will remain.

Lack of consistency between these two concepts of the family, may affect the ability to address a possible genetic risk in a family. Family feuds may limit communication amongst family members. Withholding important genetic information may even be used as a way to punish others. As noted above, a spouse, being part of the family as culture, may refuse to divulge confidential information to the genetic or biological family of a deceased spouse. In the family as biology, identical twins by having identical genetic material, have the unique situation where the genetic testing of one individual will also reflect the status of the other, so-called testing by proxy. This may disclose information, which may be unwanted by the other party, and subsequently result in an invasion of privacy.

The concept of the family as multiple families may arise in cases of unattributed paternity or paternal discrepancy, where genetic testing reveals that a specific individual has been fathered by someone other than the man believed to be the father. Bellis et al. (2005) in a review of published data from across the world, reported an incidence of paternal discrepancy which varies between 0.8% to as high as 30%. Theoretically there is also always a risk, albeit negligible, of babies being swopped at birth. Adoption and the use of donor

spermatozoa or ova also enlarge the gene pool of a particular family, creating families within families.

The importance of knowing that your family harbours a specific genetic abnormality extends beyond ethics; it has tremendous scientific value. The limitations of certain genetic tests combined with the nature of many disease-causing mutations, may manifest itself in two ways (Parker 2012, p.24). The mutation may be unique to the family, very rare or not well researched. Details of this specific mutation will assist in further genetic testing of the at-risk family members, as it would be known which abnormality to test for. Secondly, some relatively common diseases, like breast cancer, are caused by any of a large number of different mutations. Some of these may be common, well researched, and can be readily tested for. Others may be rare with no genetic tests available, unless the specific mutation is known. The importance of having this technical genetic information available, is that a potential false "negative" result based on an analysis of only the more common and known mutations, may be prevented.

There are many stakeholders in an individual's genetic material, and by disseminating that information amongst others has important biological and scientific significance at all levels of interpersonal interactions, i.e. humankind, society and family. Different motives may drive individuals to share that information with others. It may be from a purely scientific and unemotional perspective where the individual wants to contribute to the promotion of science, or someone may be altruistic and socially compelled to do so. Having said that, some individuals may view their genetic information as of a highly personal and sensitive nature, and will not allow it to be disclosed to anyone.

Families often tend to consult the same healthcare practitioner. He therefore has a professional relationship with both the index patient as well as the children and even other family members. How does he manage this dual responsibility? In some cases, like the United Kingdom, the genetic services often cut across different hospitals, with the data kept in a regional or even central facility. A genetic counsellor may identify an at-risk family based on this information. What is the responsibility towards the family members consulting such a service for genetic counselling for a particular condition, while the genetic counsellor is aware of other important genetic information of which the patient may be unaware? I

believe that the scope of a genetic consultation is such that information provided by the health care practitioner cannot be limited to one specific condition, but must be comprehensive and inclusive of all possible genetic abnormalities. The question the patient is asking, is "do I suffer from *a* genetic abnormality", rather than "do I suffer from *this or that* genetic abnormality". A fair question deserves a fair answer.

Finally, the cloud of confidentiality and privacy also extends to all members of a family known to suffer from a hereditary cancer syndrome or other genetic abnormality. In other words, the family as a group has a communal right to manage the dissemination of genetic information related to them, and whether they want to disclose this information to others.

6 Ethical issues in genetic testing

6.1 Consent

Consent plays a pivotal role in genetic testing, not only for the performance of the tests, but also regarding divulging confidential information to third parties. Consent and confidentiality are both supported by the principle of respect for autonomy, one of the four principles of biomedical ethics. It takes centre stage in the doctor-patient relationship. In the past, it was often disregarded and even ignored in line with the general attitude of paternalism and "the doctor knows best" approach. We have moved from this "doctor-orientated" approach to a "patient-orientated" approach. In modern medical practice, the patient is an important role-player in the decision-making process. However, it is also important to remember that "the duty of respect for autonomy has a correlative *right* to choose, but there is no correlative *duty* to choose" (Beauchamp and Childress 2013, p.108)

The principle of consent in genetic testing raises a number of issues. At the most basic level, that of an individual as a member of the family as biology, at least four different situations may exist:

1) consent by the index patient for genetic testing;
2) consent by the index patient for the confidential information to be divulged to at-risk individuals;
3) consent by the at-risk family member to receive the information regarding a possible hereditary genetic abnormality; and
4) consent by the at-risk family member to be tested.

There are therefore a number of related and interdependent actions, which will determine the flow of the confidential genetic information amongst family members. For instance, we need the consent of the index patient to breach confidentiality, but unless we have the consent to invade the privacy of the other at-risk family member (recipient of the information), that information remains useless to the family. If an at-risk family member not only refuses to be informed of a possible genetic risk, but also fails to pass this information onto other members of that particular branch of the family tree, like children, these

individuals are deprived from important knowledge which may influence their reproductive choices, etc. At the same time, if they were to learn about the genetic abnormality and decide to undergo genetic testing, a positive test in one of the children will indirectly reveal that the parent, who had preferred to remain ignorant of his or her status, most probably also harbours the genetic abnormality. This results in a situation of testing by proxy.

Beauchamp and Childress (2013, p.124) identify the following elements of informed consent.

I. Threshold elements or preconditions

1. Competence (to understand and decide)
2. Voluntariness (in deciding)

II. Information elements

3. Disclosure (of material information)
4. Recommendations (of a plan)
5. Understanding (of 3 and 4)

III. Consent elements

6. Decision (in favour of a plan)
7. Authorisation (of the chosen plan).

Autonomy and competency, although different in meaning, with the former based on an individual's right to self-governance and the latter emphasising that individual's ability to execute a particular task or tasks, are both based on a very similar set of criteria. The concept of competency from a medical perspective, can be viewed from two different aspects, i.e. legally and ethically. The age when an individual is regarded to be competent in the eyes of the law to consent to a procedure, is arbitrarily defined and is not necessarily always the same, depending on the type of situation or intended treatment. Section 129 of the Children's Act (2005) stipulate three different ages: above 12 years for surgical procedures, but with the parent's[15] consent; 12 years for medical procedures and without the parent's consent; and below 12 years for HIV testing and without the parent's consent. However, in all three scenarios there is an important prerequisite, i.e. "the child is of

[15] The Act also allows other individuals who act as care-givers to fulfil this legal duty depending on the type of situation.

sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the treatment/test." It is therefore obvious that even this legal definition of competence to give consent, still requires some clarification of the concepts of maturity and sufficient mental capacity. According to Beauchamp and Childress (2013, p.116) "patients and prospective subjects are competent to make a decision if they have the capacity to understand the material information, to make a judgment about this information in light of their values, to intend a certain outcome, and to communicate freely their wishes to caregivers or investigators."

Voluntariness can be explained with reference to when an individual consents to the action on his own intent, and not under the influence of another individual, society, religion or condition. Having said that, it is very seldom that any individual will not seek and take into account the opinion of other individuals, whether family or friends, in making a decision on any treatment. However, as long as that decision is based on a substantial amount of voluntariness, it can be regarded as a substantial autonomous decision. In addition, the individual may exercise his/her autonomy to appoint another individual or institution as a legitimate source of direction and decision-making (Beauchamp and Childress 2013, p.105).

Although coercion of any kind to influence a patient's decision has no ethical justification at all, even more subtle ways like persuasion and manipulation may erode a patient's ability to act voluntary. When consulting with a patient on a molecular diagnostic matter, it is important to avoid informational manipulation by presenting all relevant information in an objective, and easy to understand, manner. Genetic information is often of a highly technical nature, and may be difficult for a layperson to understand. When disclosing this technical information it must therefore be in a language, which the patient can easily understand. Genetic counsellors will usually follow a non-directive approach when recommending a plan. Medical practitioners will tend to use a similar approach than in their routine clinical practice; in other words if they tend to be more directive when normally obtaining consent in general from a patient, it is very likely they will follow the same approach when obtaining consent for genetic testing.

The disclosure of relevant information is an important element in obtaining informed consent (Beauchamp and Childress 2013, p.125). Different standards of disclosure have

been defined, with each one of these standards reflecting what is regarded as important information from different perspectives – i.e. a professional practice standard, a reasonable person standard, and finally, a subjective standard.

It is important to follow the reasonable person standard in disclosing the information, which would be regarded as pertinent or material by a reasonable person, based on the significance he or she would attach to it. In genetic counselling, we often need to incorporate some elements of a subjective standard of disclosure. By its nature, genetic information is not necessarily only about the patient, and disclosing how it may affect other at-risk family members with whom a special relationship may exist, may influence not only the patient's understanding of the disease, but also any decisions. This is very much in line with a family-centred model of autonomy "focussing on an individual's web of relationships and the harmonious functioning of the family" (Beauchamp and Childress 2013, p.109).

The basic informational elements of informed consent for cancer susceptibility testing as defined by the American Society of Clinical Oncology (ASCO) (Robson *et. al*. 2010, p.897), and which can be regarded as the professional practice standard of disclosure, are the following:

1. Information on the specific genetic mutation(s) or genomic variant(s) being tested, including whether the range of risk associated with the variant will impact medical care;
2. Implications of a positive and negative result;
3. Possibility that the test will not be informative;
4. Options for risk estimation without genomic or genetic testing;
5. Risk of passing a genetic variant to children;
6. Technical accuracy of the test including, where required by law, licensure of the testing laboratory;
7. Fees involved in testing and counselling and for DTC (direct to consumer) testing, whether the counsellor is employed by the testing company;
8. Psychological implications of test results (benefits and risks);
9. Risks and protections against genetic discrimination by employers and insurers;

10. Confidentiality issues, including, for DTC companies, policies related to privacy and data security;
11. Possible use of DNA testing samples in future research;
12. Options and limitations of medical surveillance and strategies for prevention after genetic and genomic testing;
13. Importance of sharing genetic and genomic results with at-risk relatives so that they may benefit from this information;
14. Plans for follow-up after testing.

These guidelines, and specifically point 13 of the guidelines, underline the importance of addressing any issues regarding the future dissemination of the results to any other family members who might be at risk in advance, and at the time when consent for genetic testing is obtained.

This implies that not only must consent be obtained to divulge any information of relevance to at-risk family members, but also the mechanism for how this will be achieved, needs to be discussed. This will include the role of the genetic counsellor or practitioner in possibly providing a referral letter regarding the genetic condition to family members. Such a referral letter dealing in lay terms with the condition, its risks and further management will not only assist family members, but will also ensure that the correct medical information is disseminated and will create a portal of entry for patients as well as their own practitioners if they want to source further information. This is extremely important from a scientific point of view, as knowledge of the specific mutation not only improves the accuracy of diagnosis of a genetic abnormality in other family members, but is also a much more cost-effective way of testing.

6.1.1 **Refusal to consent to genetic testing**

If a patient is competent and capable to give consent, he or she obviously has the right to withhold consent for genetic testing. This may result in the loss of the opportunity to detect a possible genetic abnormality. In practice, the clinician may have a strong suspicion of a possible hereditary genetic abnormality and share his concerns with the patient, but even

after counselling and having been informed of the potential risk to himself and his family, the patient may still refuse genetic testing.

The dilemma now arises whether the family can be informed about this potential, but still unconfirmed, risk. The first issue which needs clarification, is whether this information can be divulged without the consent of the patient, and even maybe against his express wishes. The management of this type of refusal is central to the thesis and discussed in more detail later.

The second issue is whether it is ethical to invade the privacy of the other family members with the unsolicited information about a potential, but still undiagnosed and unconfirmed, risk. How much "risk" is required to justify this breach of confidentiality and invasion of privacy? Although the guidelines published by the American Society of Human Genetics (ASHG 1998, p.474) are specifically aimed at the scenario where consent for the dissemination of information is denied, it does provide some assistance in this related scenario. The seriousness and foreseeability of the (potential) genetic condition, as well as the available measures to prevent the manifestation of the genetic risk, all need to be taken into consideration when deciding whether the information must be divulged. If there is a serious risk that one or more of the family members may harbour the hereditary genetic abnormality and effective surveillance measures are readily available to prevent the development of a malignant tumour, I believe the healthcare worker has an ethical duty to inform the potential at-risk family members.

If a histopathology specimen is available, which is usually the case after most operations, the question arises whether this specimen can be genetically analysed without the consent of the index patient. Not only will it confirm the presence of a genetic abnormality, but depending on the type of genetic abnormality, also the potential hereditary risk. At present the consent procedure, or rather the lack thereof, for the histopathology examination of tissue specimens does not include any genetic analysis of the tissue. Even though no new tissue or blood sample has to be collected from the patient for these further tests, it will still be regarded as an invasion of someone's privacy if genetic analysis is performed without the necessary consent.

Therefore, what is an alternative, albeit controversial, approach to promote the free flow of genetic information amongst family members in this stalemate situation? If it is accepted that consent to genetic testing is included in the original consent obtained for the performance of the operation and the histopathology examination of the tumour as argued in chapter 9, then obviously we will have a situation where genetic testing will automatically proceed if indicated. If no genetic abnormality is identified, this "negative" result also needs to be conveyed to the patient, and he must be advised to inform his family that there is no genetic abnormality or risk present. Not only will it assist the family psychologically in dealing with the possible fear of suffering the same fate, but it will also have potential financial implications when applying for insurance, etc.

Consent specifically related to the histopathology examination of a tissue specimen, and including all genotype and phenotype aspects of a malignant tumour, will facilitate the comprehensive analysis of the tissue specimen. This will include not only a tissue diagnosis of the type of tumour, but also whether it has a genetic association. However, the implementation of such an all-inclusive and comprehensive approach depends on the acceptance of a unified concept of the genotype and phenotype.

6.2 Confidentiality

Refusal to consent to the dissemination of genetic information to at-risk family members is a central aspect of this thesis. The main issue is whether confidentiality is absolute, or whether it can be breached in specific situations.

This debate can be opened with a to the point question: what is the point of an individual undergoing genetic testing, if the information obtained is not going to be appropriately used? The index patient has already contracted a tumour, and although some genetic syndromes may harbour a risk for more than one type of tumour, the "genetic damage" has already occurred. Why will you undergo genetic testing if the purpose is not to use this information to assist others?

The main benefits reside in the opportunity to inform (warn) the family members of a potential genetic threat and to give them the opportunity to prevent the development of disease (by undergoing prophylactic surgery), to limit the effect of disease (with regular screening to diagnose tumours in an early and resectable state), or to assist in reproductive choices. The right to confidentiality by the index patient therefore needs to be viewed against the right to beneficence and non-maleficence by the at-risk family members.

6.2.1 The *prima facie* duties of beneficence and non-maleficence

Do at-risk family members have a right to expect to be informed about possible genetic abnormalities, which may cause hereditary diseases? I use the phrase "right to expect to be informed", rather than "right to know", as the former places a stronger obligation on the index patient, and also on his health care practitioner. In practice therefore, may a health care practitioner override the refusal by his patient to divulge this information?

I indeed believe so. The at-risk family, even though they may have no contract with the patient's healthcare practitioner, may have a claim "to be rescued" under the principles of both non-maleficence and beneficence. Beauchamp and Childress (2013, p. 204) define some general examples of moral rules of obligation supported by the principle of beneficence:

1. Protect and defend the rights of others.
2. Prevent harm from occurring to others.
3. Remove conditions that will cause harm to others.
4. Help persons with disabilities.
5. Rescue persons in danger.

Based on this the at-risk family members qualify in terms of at least four of these criteria or recommendations when applied to this scenario. These recommendations can be grouped into two major groups:

1. Everyone has the right to live a healthy life (although their habits and lifestyle may not always reflect their own duty and responsibility!). Information regarding a

hereditary cancer syndrome will promote someone's health by the institution of preventive and surveillance measures.

2. There is an obligation not only to prevent harm, but also to remove conditions that will cause harm to others. In this situation the biggest threat and danger to the at-risk family member is to be ignorant and unaware of a hereditary cancer syndrome. Knowledge of such a condition is not only hugely beneficial from a health perspective, but it is also an expression of respect for the autonomy of the individual, enabling the at-risk family member to make an informed decision on how to manage the health risk.

Both specific beneficence and general beneficence apply in dealing with genetic information regarding a hereditary cancer syndrome. Specific beneficence is directed at a specific party, in this case the patient (index patient) and it is obligatory to inform the individual of all risks attached to harbouring the abnormal gene. This will include specific therapy, like surveillance for the development of metachronous tumours, which may develop at a later stage and in other organ systems. In addition, the index patient has to be informed of the risk for other family members, specifically siblings and children, to potentiality carry this same genetic trait. In practice, families tend to consult the same medical practitioner. What is the responsibility of the medical practitioner to the other family members who also happen to be his patients? I believe they are also in a position to expect specific beneficence.

Those family members who are not themselves patients of the medical practitioner, may still claim general beneficence, although it may be argued that it is of a non-obligatory nature.

We often believe that rescue situations only exist in acute life-threatening situations, like drowning. Some life-threatening situations may be of a more chronic and insidious nature. Suffering from an unknown hereditary cancer syndrome serves as such an example. With very little, if any, sacrifice from their side, the index patient and his doctor may "save" an at-risk individual by informing that individual of a possible genetic risk and the importance to be tested. As stated above, families often consult the same health care practitioner. Knowledge of a possible hereditary abnormality identified in another family member,

empowers that health care practitioner with potentially life-saving information. The only argument not to divulge this information is that the autonomy of the index patient must be respected and that privacy and confidentiality must therefore be maintained. If the index patient has refused to divulge this information to others, even after having been counselled on the potential benefits to his other family members, is the health care practitioner sacrificing any professional commitment if he then continues to inform at-risk family members? I do not believe so, and will argue that there is indeed a professional, legal and moral duty to inform the at-risk family members.

The amount of sacrifice expected from the index patient, can be illustrated by our obligations in rescue situations as discussed by Beauchamp and Childress (2013, p.206):

> Apart from very close moral relationships, such as contracts or the ties of family and friendship, we suggest that a person X has a determinate obligation of beneficence toward a person Y if and only if each of the following conditions are satisfied:
>
> 1. Y is at risk of significant loss of or damage to life, health or some other major interest.
> 2. X's action is necessary (singly or in concert with others) to prevent this loss or damage.
> 3. X's action (singly or in concert with others) has a very high probability of preventing it.
> 4. X's action would not present very significant costs, risks, or burdens to X.
> 5. The benefit that Y can be expected to gain outweighs any harms, costs, or burdens that X is likely to incur.

It is difficult to quantify the very important, but abstract, fourth criterion of "very significant risks, costs or burdens", as it will determine in the end whether an act of rescue is obligatory or not. Nevertheless, the guidance from this set of criteria is quite clear. First, the index patient has a moral duty to inform (and rescue) his at-risk family members. Secondly, failing this, the healthcare practitioner then has the duty to inform the index patient that he (the health care practitioner) will have to divulge the necessary information.

6.3 Privacy

All individuals have a right to privacy, and must be allowed to control access to different aspects of what is unique to that particular individual. This may include someone's personal space (physical and locational privacy) or relationships (relational or associational privacy) (Beauchamp and Childress 2013). Three other types of privacy are applicable to genetic information:

a) Informational privacy, as encoded in someone's genome and the information that can be deduced from these sequences.
b) Propriety privacy, as reflected by the ownership of your unique genetic code and its information.
c) Decisional privacy, allowing you to make personal choices, including whether you want to be informed of possible genetic risks in your family.

Both the privacy of the index patient and at-risk family members may be invaded. The privacy of the index patient may be invaded due to unsolicited access to the database of a genetic service or laboratory. In the era of cloud-based information technology and computer hackers, this is a real risk and needs to be managed by laboratories.

6.3.1 Privacy of at-risk family members

Informing someone about a hereditary cancer syndrome, may also be regarded as an invasion of their privacy if that information was not specifically asked for. Not everyone wants to know about genetic risks they may harbour. These individuals prefer to take their risks as life pans out. Some individuals may not wish to be informed of their familial hereditary risk at all, whilst others may want to know about these risks in their families, although they may eventually still decide not to undergo predictive testing themselves. There may be a number of psychological and emotional reasons for this decision, which may differ from person to person. Some of these, like fear of discrimination and stigmatisation,

will be discussed below. Ignorance of the possible risk to contract a disease may also be preferred in the case of some genetic diseases. If no therapeutic measures exist to reduce the risk or prevent the development of cancer or any other disease, does this knowledge really contribute to the quality of life and emotional well-being of an individual? This will differ from patient to patient. Having to cope with the impending doom of a disease still lying beyond the clinical horizon, places a substantial emotional burden on any individual and his family. Some patients prefer to follow this route of genetic ignorance and deal with their life as it pans out. Other individuals may prefer to be informed of any genetic risk, especially as it may influence their reproductive decisions and life planning.

The availability of a genetic test does not necessarily translate into widespread predictive testing by all those who may have a family history of neoplastic and non-neoplastic disease syndromes, like BRCA1 mutation and Huntington's disease respectively. Lerman *et. al*. (1997, p.414) found in their study of 149 high-risk individuals for BRCA1 mutations, that only "58% of study participants requested BRCA1 test results, and 42% declined to learn their genetic status". This reflects the significance of psychological, and specific cancer-specific, distress experience by many individuals. It is therefore important to realise that there are a significant number of individuals who do not want to know their genetic status or risks. Although this study dealt with individuals already informed of their risk, one may apply the same principles to the argument that many individuals might not want to know of any possible hereditary diseases running in his or her family. By divulging "unwanted" or "uncalled" information to an individual may result in a maleficent rather than a beneficent action due to the invasion of an individuals' privacy.

It is also possible to invade someone's "genetic" privacy by testing someone else whose result then indirectly reflects the status of the other individual. Testing by proxy, either vertical (child-parent) or horisontal (sibling, especially twins), may sometimes indirectly reveal the genetic status of another individual who prefers to remain genetically naïve. Similarly, an at-risk family member may even feel that their privacy is invaded, when contacted to be informed that a genetic abnormality has been identified in a family member. Is this invasion of privacy acceptable? It is difficult to pre-empt in advance what the decision or reaction of a particular individual will be when confronted with one of the above situations. Obviously, if the individual prefers not to be informed, this decision must be

respected. This action leads to another ethical dilemma; what about the dissemination of that information to the children of this person? Not only may it influence their own health management, but it may also influence their reproductive choices. This situation may be prevented if all family members at risk are informed separately, giving each the opportunity to make their own decisions. Again, it does not solve the whole problem. It creates another possible scenario of testing by proxy (if one of the children tests positive, it may reflect the status of the parent).

Three possible scenarios may unfold if someone with children is informed that his sibling has been diagnosed with a hereditary cancer syndrome. Hopefully the parent (the sibling of the index patient) will consent to genetic testing and depending on the result, disseminate that information to enable other at-risk family members to be counselled and tested. In the second scenario, the parent can decide that although he will inform his children of the potential risk and allow them to be tested, he himself will not undergo genetic testing. Testing his offspring may (indirectly) reveal the genetic status of the parent, because its presence in one of the children will imply that he must carry that same genetic abnormality – so-called testing by proxy. In the final scenario, the parent refuses not only his own genetic testing, but also refuses to pass the information on to his children. This important information is therefore loss to that particular branch of the family

6.4 Summary

It is obvious that informed consent not only plays a central role, but also the single most important role in the management of genetic information. It involves different aspects and covers a whole spectrum, ranging from consent for genetic testing to consent for divulging genetic information as well as consent to invade someone's privacy. Hopefully, in the ideal world, consent will always be granted, allowing all these actions to occur and thus facilitate the free-flow of important and potentially lifesaving information.

Refusal of consent, however, highlights the uniqueness of hereditary diseases, including cancer syndromes. In routine medical practice we apply the principles of respect for autonomy, beneficence, non-maleficence and justice while focussing on a specific individual

– our patient. Our *prima facie* and actual duties are determined solely by the interest of that individual and his particular circumstances.

In genetic practice we are no longer dealing with only one individual, nor the masses catered for by public health policies. Similar to a HIV-infected individual refusing to inform his sexual partner, we do have an obligation to other at-risk family members. Our ethical and moral responsibilities to different individuals linked together through close interpersonal relationships, can be represented by a number of overlapping Venn diagrams. Each of these represents an at-risk family member and with each one of them expecting the same – respect for autonomy, beneficence and non-maleficence. It is our duty as healthcare workers to solve any stalemate position due to a lack of consent, to generate the maximum benefit to all the involved individuals.

7 Refusal to disclose genetic information

Before we discuss the main reasons behind the refusal by index patients to grant consent to disclose genetic information, it is important to define the extent of the problem. Although no specific statistics could be find, an article by Falk *et. al*. (2003) does provide some idea how often this dilemma may occur in clinical practice.

7.1 Incidence of refusal to divulge information

In a study conducted by Falk *et. al.* (2003), 206 medical geneticists participated in a survey addressing the issue of refusal to inform at-risk family members. 60% of the 206 individuals whom participated had encountered patients who refused to notify at-risk relatives. The number of encounters varied: 45% of this group encountered refusal on 1-5 occasions, 38% on 6-15 occasions, while 11% of this group encountered it on more than 16 occasions. Reasons cited by patients for not being willing to notify their at-risk relatives include: "concern of insurance discrimination, concern of employment discrimination, concern of altering family dynamics, (and) estranged family relationships" (*ibid*., p.377). In a substantial number of the cases the medical geneticist was not aware of the patient's reason.

It appears that although patients may initially have reservations to divulge the information to at-risk relatives, only a very small number of them will persist with their refusal. The incidence of index patients refusing to pass on information to their at-risk relatives is therefore low; however, as with most ethical issues in medicine, the dilemma is not in the number of cases involved, but in what is right or wrong. The main reasons for refusal are based on fears for discrimination and stigmatisation, including by those family members who will directly benefit from the information.

7.2 Discrimination

One of the major concerns in disclosing genetic information is the possibility that this information may be used to discriminate against individuals as far as employment prospects and insurability are concerned. In this regard, even the mere fact that someone (or one of his family members) had undergone genetic testing in the past, may result in the individual being penalised. This may occur even though the insurer may not know the result of the genetic testing, which may even be a negative result. I believe that just the fact that there has been a possibility of a genetic disease in a family, may be enough grounds for an insurance company to load the premium or to exclude certain conditions.

It is important that any potential discrimination based on genetic status must be governed, if not prohibited, by legislation. Although legislation exists in most first world countries to prohibit the use of genetic information as a basis for discrimination, it still does not provide absolute protection, as insurance companies circumvent this by using family histories to base their decisions about risk on.

7.2.1 South Africa

In South Africa, no specific legislation dealing with discrimination based on genetic testing exists, but a number of acts, like the Employment Equity Act (1998) and Medical Schemes Act (1998), do make indirect reference to genetic information and its potential discriminatory abuse as part of the management of medical information in general. In addition, the Constitution of the Republic of South Africa (1996) and other common law principles further support the right of a person not to be discriminated against. Section 9 of our Constitution deals with equality, and states *inter alia* that the State or another person may not unfairly discriminate against someone. The issue will be whether a higher insurance premium or other penalty, like exclusion of certain benefits, is deemed to be regarded as unfair discrimination.

South Africa has very strict privacy laws in place; some of these laws have been promulgated, but not yet implemented. Section 14 of the Constitution and the common-law right to privacy include privacy of information; that is, the right to determine for oneself

how and to what extent information is communicated to others. Computer-based genetic registers are subject to the Promotion of Access to Information Act (2000). Although the recently promulgated Protection of Personal Information Act (2013) aims to protect personal information, section 32 creates some confusion. This section allows for the processing of personal information concerning inherited characteristics if a serious medical interest prevails. Although the aim of this section is most probably to allow the use of this information by medical practitioners and health care facilities, it does not exclude insurance companies, medical schemes and other institutions whose interest in someone's genetic information may not share the same honest intentions.

In a document published by the Sub-directorate Human Genetics of the National Department of Health (nd., p.50) section 9.1.6 states, "individual privacy should be protected from institutional third parties, such as employers, insurers, schools, commercial entities, and government agencies". Family members do not form part of this group of third parties; whether this is intentional or not, is not obvious, but it therefore does not legally and specifically prohibit the disclosure of information to family members.

Which particular law other than the Constitution will take preference is a legal debate; from an ethical perspective the medical doctor must ensure that confidentiality is maintained at all times, unless authorised otherwise by the patient. Having said this, we must remember that confidentiality is not absolute, especially where other identifiable third parties may be at risk, as discussed elsewhere in this document.

7.2.1.1 Employment

Businesses are forced to operate cost-effective and efficient in a free market economy. Genetic screening of (potential) employees provides the employer with an opportunity to reduce the healthcare costs of the workforce. This may be justified when it seems to be to the benefit of the employees. An employer may for instance want to screen candidates, to exclude those susceptible to either occupational or non-occupational diseases (MacDonald and Williams-Jones 2002).

At the same time, it creates the risk to introduce eugenics in the workplace, as certain genetic traits may be regarded as more suitable for managerial and other senior positions in a company. This will create different class orders amongst the economically active workforce based on genetic disposition. At the same time, the State will have to carry the burden to support the "genetically unemployable" of society.

The medical testing of employees and applicants for employment is prohibited by section 7 of the Employment Equity Act (1998), unless "(a) legislation permits or requires the testing, or (b) it is justifiable in the light of medical facts, employment conditions, social policy, the fair distribution of employee benefits or the inherent requirements of the job". According to this, genetic testing as part of the routine occupational health services may have a role to play if a specific genetic abnormality or trait may be an exclusion factor for employment.

MacDonald and Williams-Jones (2002, p.238) suggest that if a number of criteria are met, it would be ethically permissible to offer workplace genetic testing. However, it cannot be compulsory. Some of these criteria include the use of only highly specific and sensitive genetic tests, testing for genes not associated with a historically disadvantaged group, as well as the guarantee of continued access to group insurance. Offering these services may be important to protect the welfare of the workforce. Certain genes may increase susceptibility to environmental factors and toxins to be found in a particular workplace. These may include an increased risk to develop bladder cancer when individuals with a particular N-acetyltransferase phenotype are exposed to carcinogenic arylamines. It is also suspected that certain genetic traits may increase the risk for serious brain injury and even Alzheimer's disease in contact head injuries; this may affect the employment of professional sportsmen participating in contact sport.

7.2.1.2 Insurance

The insurance industry in South Africa consists of a whole spectrum of services, including life insurance as well as the medical aid industry or "health funders". Insurers are by nature risk-aversive. Actuaries constantly try to determine the risk associated with potential clients and diseases to be in a better-informed position to allocate premiums. Alternatively, some health conditions may be excluded from the list of benefits.

Kinsley (2009) addresses the use of genetic information by insurance companies in South Africa, and highlights the risk for genetic discrimination. This may create a "genetic underclass" or a group of "genetically impaired" individuals. The repercussions for these individuals with genetic predispositions to certain diseases are that they may not be granted health insurance at all, or may be charged higher premiums. It has to be borne in mind that the Medical Schemes Act (1998), provides that a registered medical aid scheme may not unfairly discriminate directly or indirectly against its members based on their "state of health".

Insurers have argued that using genetic information to predict risks is nothing more radical than an extension of their current risk-assessment practices (Kinsley 2009). At present, insurers require applicants to not only provide detailed information regarding their own medical history and lifestyle, but also their family medical history. It appears that any information obtained from genetic tests forms part of the risk profile of the individual.

The existence of certain single gene disorders can predict to some extent the risk for the development of a genetic disease or lowered life expectancy. However, factors like the penetrance and variance of the genetic abnormality also need to be taken into account. It is not always that obvious to what extent and accuracy a genetic test predicts the onset of the disease, and how to factor this information into any actuarial estimate. If the multi-factorial and polygenic nature of many diseases, as well as other factors, like penetrance, is not taken into account, it will predispose to discrimination in the insurance industry. Kinsley (*ibid.* p.92) believes that this situation may be somewhat avoided if genetic specialists assist the industry "in converting genetic information into a predictive risk for life insurance underwriting purposes".

Otherwise, the question will be asked whether the insurance industry has the ethical backbone to regulate the application of genetic information in a non-discriminatory manner, or whether it must be regulated by statute.

7.2.2 Rest of the world

The United States of America have promulgated a couple of laws regulating the use of genetic information, including the Genetic Information Non-discrimination Act (2008) (GINA) which protects against discrimination based on genetic information by the health industry and employers (Robson 2010, p.898). The main action points of this act are as follows:

1. It prohibits health insurance carriers from:

a. denying coverage because an individual took or refused to take a genetic test;

b. denying coverage based on tests results;

2. It prohibits employers from using this information as the basis for employment decisions.

The Standards for Privacy of Individually Identifiable Health Information (Privacy Rule) promulgated under the Health Insurance Portability and Accountability Act (1996) and the Americans with Disabilities Act (1990) also protect genetic information and the abuse thereof for discriminatory purposes (Storm 2008).

7.3 Stigmatisation

Few other institutions are as feared as the court of public opinion. Although hereditable cancer syndromes, like any other dreaded disease, will most likely be viewed with empathy and compassion, genetic diseases may have a social stigma attached to it. This may be either due to the physical effects, like neurofibromatosis resulting in elephant-like features, or socio-behavioural manifestations, like Tourette syndrome.

In the family context where a mutation has been transmitted to a child, the responsible parent may experience guilt, while the child may react with anger and even blame the parent for not fulfilling his parental responsibilities.

Someone's religious beliefs may also play a role in whether they would allow the dissemination of genetic information. If they believe it may result in the termination of

affected pregnancies by other family members, they may be concerned of being stigmatised or ostracised by their religion if seen as indirectly promoting abortions.

Withholding important genetic information from at-risk family members may also be used as an agent to punish other family members, especially in a dysfunctional family.

8 Legislation, professional guidelines and legal precedent on consent, confidentiality and the duty to disclose

8.1 Legislation

South Africa does not have legislation that deals specifically with the management of genetic information. However, some guidance can be found in statutes, like the National Health Act (2003). In addition, the professional guidelines published by the Health Professions Council of South Africa (which are in the process of being updated), are also of some assistance. Scenario's, like deceased persons, individuals not competent or able to give consent, vulnerable groups, as well as research subjects, will not be discussed in detail although each has specific legal and/or ethical requirements.

Section 6 of the National Health Act (2003) defines the extent of the information that has to be conveyed to the patient when obtaining informed consent:

> (1) Every health care provider must inform a user of-
>
> (a) the user's health status except in circumstances where there is substantial evidence that the disclosure of the user's health status would be contrary to the best interests of the user;
>
> (b) the range of diagnostic procedures and treatment options generally available to the user;
>
> (c) the benefits, risks, costs and consequences generally associated with each option; and
>
> (d) the user's right to refuse health care.

It may be argued that section 6(1)(c) places a legal obligation on the health care worker at the time of obtaining informed consent for genetic testing, to inform the patient that disseminating relevant information to at-risk family is seen as a consequence of genetic testing.

In the case of children, two sections of the Children's Act (2005) are relevant. Section 9 states that, "in all matters concerning the care, protection and well-being of a child, the standard that the child's best interest is of paramount importance, must be applied."

Genetic testing can be regarded as "medical treatment", and according to section 129(2):

> a child may consent to his or her own medical treatment or to the medical treatment of his or her child if -
>
> *(a)* the child is over the age of 12 years; and
>
> *(b*) the child is of sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the treatment.

It is important that these two sections be read together, as there may be circumstances where it may not be to the benefit of a child to undergo genetic testing, for instance where that may determine whether the child is genetically suitable for adoption. In such a scenario section 9 of the aforementioned act, as well the constitutional rights of children will supervene. The same applies to genetic testing in children to identify adult-onset diseases.

Finally, what is the position of minor children if their parents refuse to inform them of a hereditary cancer syndrome? Fortunately, most inherited cancer syndromes only manifest in adulthood; it is therefore important to have a system in place to inform these children and have them tested when they are regarded legally capable to consent. An omission to inform the at-risk daughter of a patient who died from colon cancer as a result of familial polyposis formed the basis of the case, *Safer versus Estate of Pack* (discussed later). As genetic testing is regarded as a medical and not surgical procedure, this can be done according to the Children's Act (2005) when the child is twelve years and older and mentally competent.

From a moral perspective, it is important to differentiate between diseases, which may already present or manifest in early adulthood and for which screening procedures need to be instituted during childhood, like familial adenomatosis polyposis which carries a high risk for the development of colon cancer, and those diseases which are of adult-onset. In the latter group, if no preventative or curative measures can be instituted, this knowledge may not be in the best interest of the child. Knowing that a particular child is harbouring a

specific genetic abnormality may influence the way he is seen as a member of the family, including investment in his future development, etc.

The statutory position on confidentiality is addressed in section 14 of the National Health Act (2003), which states:

> (1) All information concerning a user, including information relating to his or her health status, treatment or stay in a health establishment, is confidential.
>
> (2) Subject to section 15 [governing access to health records], no person may disclose any information contemplated in subsection (1) unless-
>
> (a) the user consents to that disclosure in writing;
>
> (b) a court order or any law requires that disclosure; or
>
> (c) non-disclosure of the information represents a serious threat to public health.

Section 14(2)(c) of the above act refers only to the disclosure of confidential information if a "serious threat to public health" exist. This will include the threat of communicable diseases, like tuberculosis. However, the individual (or any other grouping other than "public", including family) is excluded from this definition. Therefore, it appears as if there is a statutory exclusion, which might even be interpreted as a prohibition, to inform individuals who may be at risk without the consent of the patient. Whether this position will be upheld in a court of law, especially taking other legislation like our Constitution into account, is doubtful.

The only other South African legislative or governmental publication specifically addressing the issues of consent and confidentiality in genetic testing, appears to be a document published by the Sub-directorate Human Genetics (which forms part of the Maternal, Child, Women's Health and Nutrition Cluster) of the National Department of Health (n.d., p.50). Section 9.1.5. states that "confidentiality of genetic information should be maintained except when there is a high risk of serious harm to family members at genetic risk and the information could be used to avert this harm." In section 9.2., addressing the ethical

principles for genetic professionals, this is re-emphasised with terms like, “honour the confidentiality of information, shared in the relationship with patients and their families” and “urge patients and families to share genetic information, with relatives at risk, pointing out the possible need for this, early in the relationship”. This is reiterated in the summary on confidentiality, where the issue of reproductive choices is also brought into the quotation:

> In genetics, the true patient is a family with a shared genetic heritage. Family members have a moral obligation to share genetic information with each other. If children are intended, individuals should share information with their partners.

8.2 Professional guidelines

What is the position of professional bodies on the disclosure of familial genetic information without consent and against the wishes of the patient? It appears as if both the American and British views are the same and that confidentiality is not absolute.

The American Society of Human Genetics (ASHG) (1998, p.474) has stated that: “disclosure should be permissible where attempts to encourage disclosure on the part of the patient have failed; where the harm is likely to occur and is serious and foreseeable; where the at-risk relative(s) is identifiable; and where either the disease is preventable/treatable or medically acceptable standards indicate that early monitoring will reduce the genetic risk.”

However, I differ from the last requirement by the ASHG for the disclosure of genetic information. Obviously, some genetic diseases cannot be prevented and with no treatment options available may, or even will, cause disease. Huntington’s disease is an example of the latter. Even in the case of Huntington’s disease, where there is not much to be done to change the natural course of the disease, knowledge of such information may still help the individual (and his family) to prepare for the illness. This may include the creation of a psychological support system for the family to deal with the looming illness, as well as long-term financial planning. It may also affect the reproductive choices of other at-risk individuals.

The Joint Committee of the Royal College of Physicians, Royal College of Pathologists and the British Society for Human Genetics (2011, p.22) stipulates that the rule of confidentiality is not absolute, and that it may be justified in special circumstances to "break confidence where in doing so a serious harm can be avoided." They suggest that as part of this process the patient needs to be informed that confidence will be breached and the information will be disclosed. Discussions with experienced professional colleagues and documentation of the reasons to breach confidentiality must form part of this process.

It is interesting to note that there are countries, like Norway, Switzerland and France, where confidentiality is regarded as absolute, and where no information may be divulged against the wishes of a patient (American Society of Human Genetics 1998).

Professional guidance in South Africa is provided by the guidelines published by the Health Professions Council of South Africa. Two sections are of relevance in this matter (Health Professions Council of South Africa, 2008b, p.11):

> 17.1 Screening or testing of healthy or asymptomatic people to detect genetic predispositions or early signs of debilitating or life threatening conditions can be an important tool in providing effective care. However, the uncertainties involved in screening or testing may be great, for example the risk of false positive or false negative results. Some findings may potentially have serious medical, social or financial consequences not only for the individuals, but also for their relatives. In some cases, the fact of having been screened or tested may itself have serious implications.
>
> 17.2 Health care practitioners must ensure that anyone considering whether to consent to screening or testing can make a properly informed decision. As far as possible, practitioners should ensure that screening or testing is not contrary to the individual's interests. Health care practitioners must pay particular attention to ensuring that the information the person wants or ought to have is identified and provided. Practitioners should be careful to explain clearly:

17.2.1 The purpose of the screening or test;

17.2.2 The likelihood of positive or negative findings and the possibility of false positive or negative results;

17.2.3 The uncertainties and risks attached to the screening or testing process;

17.2.4 Any significant medical, social or financial implications of screening or testing for the particular condition or predisposition;

17.2.5 Follow up plans, including the availability of counselling and support services.

It can be argued that although “any significant social implication” refers to the risk of stigmatisation and discrimination, it also includes the responsibility of the patient to inform others who may be at risk. As the information forms part of the counselling process to obtained informed consent, it places an ethical responsibility on the health care practitioner to inform the patient beforehand of the need to notify at-risk relatives.

Although no particular reference is made regarding the concept of confidentiality when dealing with genetic information, the general principle that confidentiality is not absolute, is reflected in the following (Health Professions Council of South Africa, 2008a, p.6):

8.2.4 Disclosures in the public interest:

8.2.4.1 In cases where health care practitioners have considered all the available means of obtaining consent, but are satisfied that it is not practicable to do so, or that patients are not competent to give consent, or exceptionally, in cases where patients withhold consent**,** personal information may be disclosed in the public interest where the benefits to an individual or to society of the disclosure outweigh the public and the patient's interest in keeping the information confidential, (e.g. endangered third parties such as the spouse or partner of a patient who is HIV positive, who after counselling refuses to disclosure his or her status to such spouse or partner; or reporting a notifiable disease).

8.2.4.2 In all such cases the health care practitioner must weigh the possible harm (both to the patient and to the overall trust between practitioners and patients) against the benefits that are likely to arise from the release of information.

8.2.4.3 Examples of circumstances to protect the patient or other persons from death or serious harm, include, but are not limited to:

a. Access to prophylactic treatment for a person who has had contact with an infectious disease, or

b. An employee with a health condition, which may render him or her unable to work safely posing a danger to co-workers or clients

c. A driver of a vehicle who requires medication to control an illness that might impair his or her driving ability.

8.3 Legal precedent

No specific legal precedent or case law exists in South Africa regarding the legal obligation, if any, of a patient or health care practitioner to inform an at-risk relative of the findings of genetic analysis. In the United States, reference is usually made to three cases (American Society of Human Genetics Social Issues subcommittee on Familial Disclosure 1998; Harris 2005; Schneider 2006; Storm 2008).

The most well-known case in bio-ethics dealing with the conflict between the right of privacy and confidentiality of an individual versus the duty to warn an identified individual of a foreseeable and serious harm, is the case of *Tarasoff versus Regents of the University of California*. This case deals with the general duty to warn a third party of possible danger or harm, and is supported by the principles of beneficence and non-maleficence. Authors like Harris (2005) believes that this situation differs from a case when the risk is genetic, and not infectious or an instance of physical harm; in the former situation the patient does not directly pose a harm to the relative(s) as the mutation is already either absent or present in

the relatives. It is therefore more of a moral duty rather than a legal obligation to inform others.

Two American cases addressing the legal duty to warn third party relatives of genetically inheritable diseases have divergent views. In *Pate versus Threkel*, the Florida Supreme Court ruled in 1995 "that a physician's duty to warn about a cancer predisposition syndrome was satisfied by educating the patient about familial cancer risk" (Storm 2008 p.229). In this case, dealing with a patient with medullary carcinoma of the thyroid, genetic risks were distinguished from infectious diseases or physical harm, in line with Harris's argument.

In 1996 the New Jersey Appellate Court in *Safer versus Estate of Pack* ruled that a medical practitioner has a broader duty to warn, and "that a physician's duty to warn extends to identifiable third parties known to be at risk of avoidable harm from a genetically transmissible condition, and that physicians should take 'reasonable steps' to warn at-risk family members" (*ibid.*). This was a case of familial adenomatous polyposis, and in this matter the court found "'no essential difference' between the type of genetic threat at issue in this case and 'the menace of infection, contagion, or a threat of physical harm'"(*ibid*).

9 The justification for a comprehensive consent for the histopathology examination of specimens, which will facilitate the genetical analysis of tumours

My first argument is that the current way in which clinicians obtain consent for an operation, is no longer adequate and needs to be supplemented with a comprehensive and all-inclusive consent for the histopathology examination of a specimen. At present, the consent process only focuses on the surgical procedure, and seldom takes any aspects surrounding the histopathology examination of the tissue specimen, including genetic analysis, into consideration. This creates the potential situation where the histopathologist may proceed with investigations without the consent of the patient, which although not necessarily diagnostic of a hereditary cancer syndrome, may identify those with a real risk to suffer from a genetic abnormality.

The need for a comprehensive histopathology consent procedure is based on the following two arguments, with the conclusion of the first argument also serving as a premiss for the second argument.

9.1 The argument supporting a unified concept of the genotype and phenotype

Premiss: Pathology investigations exist today to determine a “mixture” of genotypic and phenotypic features at any point along the genotype – phenotype continuum of a tumour.

Conclusion: The concepts of the genotype and phenotype of a tumour are no longer two separate entities, but have merged together from a scientific analytical perspective.

9.2 The argument supporting a comprehensive and all-inclusive consent for histopathology procedures

Premiss 1: Patients have a right to respect for autonomy, and this requires that informed consent is obtained for any pathology investigation.

Premiss 2: The concepts of the genotype and phenotype of a tumour are no longer two separate entities, but have merged together from a scientific analytical perspective.

Conclusion: Informed consent obtained for the histopathology examination of a tumour specimen must be comprehensive and all-inclusive of morphological and genetic testing.

9.3 Implementation of a unified concept of the genotype and phenotype

As already stated, the consent process at present focuses primarily on the surgical procedure and the possible complications thereof; there is often only one paragraph on the consent form dealing with the "disposal" of tissue. The latter implies either the histopathology examination of the tissue specimen, or in the case of amputations, etc. the cremation or disposal otherwise of the tissue.

Patients seldom, if at all, give specific and express consent for the histopathology procedures to be performed. This is highlighted by the fact that patients sometimes complain that the specimen was submitted for histopathology examination without their knowledge and permission, and they are now confronted with an (unexpected) pathology bill.

I believe that specific, detailed and comprehensive consent for histopathology procedures may not only solve some of these "administrative" issues, but also more importantly, if properly obtained, will be of tremendous benefit to the patient from a medical and health perspective. This is required, as we have to accommodate the impact of modern science, and in particular molecular pathology and genetics, into the way we practise histopathology

and medicine in this modern era. The incorporation of all histology and non-histology information into an "integrated diagnosis" will soon form part of the next World Health Organization (WHO) classification of central nervous system tumours (Louis *et. al.* 2014). In time, our ability to predict the risk to develop disease or malignancy will become part of everyday medical practice, and we must be careful not to end up in a stalemate position where bio-ethical issues prevent us from using this information to benefit humankind.

Scientific and laboratory techniques, like immunohistochemistry, gene expression profiling, sequencing, etc. are all changing the concepts of phenotype and genotype. In addition, we also realise that other factors, like epigenetics, play an important role how the genotype will influence, rather than determine, the phenotype. If we accept that the phenotype and genotype are merging, then we must start to treat them like one concept, at least as far as consent is concerned. The pathology examination of any tumour must include all aspects of that tumour, i.e. the morphological features as well as somatic and germline genetic information, and the (potential) extent of the investigations must be conveyed to the patient when informed consent for the procedure or operation is obtained.

If the genetic information of an individual no longer has "special standing" in medicine, but is merely seen as an integral component of the genotype-phenotype continuum, it may be argued that any consent obtained for the analysis of a specimen is all-inclusive. In practice, if a patient is operated on for colon cancer, consent for the analysis of the tumour specimen will therefore include any genetic analysis deemed necessary to determine *inter alia:* 1) the diagnosis and classification of the tumour, 2) identifying possible therapeutic opportunities (pharmacogenomics), and 3) any genetic abnormality which predisposed the individual to the development of the tumour. The latter is the controversial issue at stake, as it will extend genetic analysis beyond the identification of somatic mutations. It will also diagnose germ-line mutations, and therefore identify a family at risk.

In the oncology setting, knowledge regarding an underlying genetic abnormality has definite benefits to the individual patient. Many of the hereditary cancer syndromes affect more than one organ system (see annexure A for a list of tumours associated with Lynch syndrome). By identifying a germline mutation, the index patient can be more thoroughly monitored and screened for the development of metachronous tumours in the colon or

other organ sites. These genetic tests are therefore at the time of diagnostic work-up for the sole benefit of the index patient. In neglecting to perform these tests, the histopathologist may not be fulfilling his professional duty to the patient.

The opposite argument is that a staggered consent process needs to be followed. This approach will, however, not solve the fundamental problem of how far histopathology testing can proceed, before additional consent for genetic testing is required. In addition, as discussed earlier, there is a real risk that this fragmented approach may result in the loss of important information in the post-operative setting during the referral form one specialist to another, e.g. oncology.

9.4 A proposed informed consent procedure for histopathology procedures

I believe that all these problems can easily be addressed by widening the scope of the consent obtained at the time of surgery. This must be an all-inclusive and comprehensive consent at the time of the operation, which will enable the histopathologist to conduct a detailed histopathology analysis, and if indicated, genetic study of the submitted tissue specimen.

The informed consent procedure at the time of surgery must be based on two separate consents to be obtained:

1) Informed consent related to the surgical procedure, including the anaesthetic procedure and possible complications. At present, this is the standard procedure.

2) Informed consent related to the histopathology examination of the tissue specimen. This must include not only consent for the morphological examination of the specimen, but also consent for further genetic testing of the specimen if deemed necessary. Although the patient must be given the option to indicate whether he would prefer a staggered process, i.e. consenting to any germ-line genetic testing only after being informed of, and counselled, on the need for these tests, there must

> be no opt-out option. Throughout these procedures to obtain consent for histopathology and genetic testing, the potential need to divulge any beneficial information regarding genetic syndromes to at-risk family members must be emphasised. At present consent is seldom obtained for any laboratory investigations, except HIV testing, and the patient usually will only give implied or tacit consent when told that the specimen will be sent to the laboratory for examination. As stated before, this standard of practice often also applies to clinical pathology specimens, like blood, and is not the ideal medical practice.

This is the only way for all scientific information in a tissue specimen to be optimally harvested for the benefit of the patient, and (hopefully) the family. If the proposed histopathology classification system for central nervous system tumours (and soon other organ systems) is implemented in the near future, genetic information will become a requirement as part of the diagnosis. Our bio-ethical approach must be supportive of our evolving scientific concept of diseases. This brings us to the next part of the discussion, specifically whether the family has any propriety or other rights to this genetic information.

10 Moral perspectives on the management of genetic information in hereditary cancer syndromes

My second, and also my major, argument is that information regarding a possible hereditary cancer syndrome cannot be withheld from other at-risk family members on request of the index patient (or designated decision-maker). In fact, I would like to argue that the information does not even belong to the family as such, but to society and humankind at large. As long as the privacy of the family harbouring a specific genetic abnormality can be protected and confidentiality maintained, application of this scientific information to be of universal benefit, must be allowed.

BRCA1 and BRCA2 genetic mutations in breast cancer serve as an appropriate example to illustrate the mutual benefits that can be reaped from the free and unhindered flow of genetic information amongst all levels – humankind, society, family and the individual. On a global level, the pooling of genetic information in patients suffering from breast cancer has enabled us to identify the most common mutations affecting humankind. It was also noted that certain social groups, like the Afrikaner group in South Africa, are more prone to harbour specific mutations. This emphasises the importance of societies sharing a common genetic heritage. Finally, certain families may have genetic mutations unique to that family and which may therefore be relatively rare. These mutations may not necessarily be diagnosed if the specimen is subjected to routine genetic testing. If the exact nature of the mutation is known, specific analysis of that genetic sequence can be performed, which will not only increase the sensitivity of the analysis, but will also be at a much lower cost to the patient.

10.1 Introduction

The two main moral and ethical issues central to the discourse regarding ownership of genetic information are confidentiality and privacy. These two issues form the crux of the matter.

In the modern world, our perception and definition of privacy is constantly changing. Some of these may be as a result of new technology, like the tracking facility on mobile phones which enables us to digitally explore services and places in our geographical and spatial vicinity. In exchange for security, we may also allow an invasion of our privacy by surveillance equipment. The above invasion of our privacy is tolerated and consented to on condition that we receive some benefit in exchange: information, security, etc. At the same time, we are also experiencing a cultural change that is referred to by Chadwick *et. al*. (2014, p.13) as the "new exhibitionism", driven by the proliferation of social media. We are more and more willing to voluntarily lower the fences surrounding our private lifes on websites like Facebook, even entering into intimate digital relationships with individuals we have had very little, and sometimes even no, physical contact with. This is all happening with our consent, usually with the click of a mouse or a tap on the screen, and without us always really understanding the extent and implications of what we are consenting to. One may thus argue that even though we are consenting to all these applications and social websites, we are often ill informed and oblivious to the potential threat this may have on our personal lifes.

With this often public flow of personal information amongst "contacts", one would assume that individuals would also be more readily sharing information regarding their medical, including their genetic, status. However, it appears as if individuals are not only maintaining the *status quo* in the management of medical information, but that the awareness of bio-ethical rights and duties has subjected the governance of information of such a nature to even stricter rules. Initiatives, like biobanking, have also brought new challenges to privacy and data protection, especially in view of the globalisation of medical information.

Man, most probably as part of a primitive survival trait, has always been an "opportunistic animal". If the release of certain information may have positive spin-offs, like sympathy, security or social popularity, we are often more than willing to share it. At the same time, we still want to control the type and amount of information we divulge to others. We tend to protect any information that we believe may harm us. This may differ from individual to individual, and it is also influenced by our culture and society. In this modern age, we all strive to project that perfect image - physically, emotionally and professionally. We are well

aware that society usually does not deal favourably or sympathetically with the losers of life's lotteries.

In the genetic context, this potential harm may include discrimination by employers and insurers, stigmatisation by society and even family members, and ultimately social exclusion, rejection and expulsion. To prevent this, we often adopt an exclusive position to protect "negative" medical information, like HIV status and hereditary genetic information, from society. However, there are many who choose to publish their genetic data in the public domain. Chadwick *et. al.* (2014, p.57) refer to two websites creating a virtual forum for patients, i.e. *patientslikeme.com* and *quantified self*.

Although professional guidelines, including the best medical practice guidelines, and legal precedent exist and have already been discussed elsewhere, we still need to reflect on the moral and ethical position related to the ownership of genetic information.

Like with any other bio-ethical dilemma in medicine, the issue of ownership of genetic information about hereditary cancer syndromes can be viewed from the perspective of different moral and ethical theories. These theories may emphasise different aspects and offer different approaches and solutions to the dilemma, and even be in conflict with one another. Like in many other clinical situations in medicine, none is necessarily sufficient enough to be our sole moral and ethical compass.

I believe that virtue ethics, and specifically the ethics of responsibility based on the virtue of *phronesis*, is the most appropriate moral theory to guide the healthcare practitioner when dealing with bio-ethical issues in everyday modern practice. This includes the situation when confronted with the ethical dilemma of divulging confidential information against someone's wishes or invading someone's privacy. I will argue this position in more detail below.

Three other major theories and/or bio-ethical approaches, i.e. utilitarianism, deontology and the four principles of biomedical ethics as defined by Beauchamp and Childress (2013), will also briefly be discussed. The main purpose of the discussion on these three theories is to establish their relevance for this discourse, and in particular to identify any serious

conflict and contradictions which may exist amongst these different moral approaches as well as to identify some common ground.

Other theories – libertarianism, egalitarianism, communitarianism, the ethics of care and casuistry - also have some aspects that may be applied to the deliberation, but these will not be dealt with in any detail, except for some passing comments. Even the individual freedom granted by liberal individualism is not absolute and unqualified. Confidentiality, as an exercise of our right to autonomy and therefore our individual freedom, is still limited to the extent that it may sometimes be overridden if such infringement on the rights of an individual is justified to prevent harm to others. In the African context of *Ubuntu*, it may well be argued that communitarianism automatically places genetic information in the public domain, at least for the family. At the same time, cultural prejudice and beliefs in the African communities regarding the origin of disease may ostracise the individual harbouring the genetic abnormality.

10.2 Virtue ethics

10.2.1 **Introduction**

The central focus of virtue ethics is the character of the person. Although Aristotle said "that a virtue is a trait of character manifested in habitual action", Rachels and Rachels (2012, p.159) give a more refined definition: "a moral virtue is a trait of character manifested in habitual action, that it is good for anyone to have." This not only distinguishes it from vices (which are also character traits), but also brings a distinction between "moral" and "general" virtues. A virtue can also be regarded as the mean or midpoint of the range between two vices, e.g. courage as the mean between the two extremes of cowardice and foolhardiness. Prudence can be regarded as the midpoint between the vice of recklessness and the vice of avoiding danger at all costs (Van Niekerk 2011, p.31).

"In Aristotle's view the right act is that which a virtuous person would do in the circumstances" (Hope *et. al.* 2003, p.9). "The virtues are those characteristics that will ensure that those endowed with them will have the best life overall. The best life, for

Aristotle, is that associated with *eudaemonia,* often translated as flourishing" (*op. cit*.) This flourishing, according to the above authors "can perhaps be seen as a kind of deep happiness, which is less connected with the pleasures than is the concept of happiness, or wellbeing, used to underpin utilitarianism." Although it may be seen as a selfish or egoistic theory, as it emphasises one's own flourishing, most virtues are not selfish. In fact, virtues like generosity and kindness will benefit those others in the immediate sphere of existence of a virtuous person. For me, flourishing is that deep sense of happiness and moral contentment experienced by the virtuous person upon the realisation of his moral actions. Although some interpersonal and intercultural differences may exist amongst the different virtues, some are universal and inherent to all moral agents – like honesty, generosity, courage.

Virtue ethics is often said to have two selling points (Rachels and Rachels 2012, p.167). Firstly it supports moral motivation. We do not only do things because of an abstract sense of duty or from a desire to do the right thing. We do it because we have a sincere desire[16] to do so, "and virtue is its own reward (Hope *et. al*. 2003, p.9). Secondly, although impartiality is a dominant theme in modern moral philosophy, for instance utilitarianism, some virtues are partial rather than impartial. The partial virtue of loyalty to our loved ones and friends, recognises and gives meaning to our special relationships.

10.2.1.1 Possible criticism against virtue ethics.

Like any other moral theory, virtue ethics is not immune to criticism. Some criticisms are aimed at the following:

1. It may not be able to effectively guide action. Oakley (2012, p.99) doubt "whether the notion of virtue is clear or detailed enough to serve as the basis of a criterion of rightness".

2. The plurality of virtuous character traits is a potential problem as not all cultures and people may respond in the same way in similar situations. Virtues and the

[16] In Afrikaans the word "hartsbegeerte" would be appropriate to emphasise the sincerity of this desire.

interpretation thereof may differ from person to person, and from culture to culture. Some virtues, like loyalty, may even be associated with unethical behaviour, like gangsterism (Beauchamp and Childress 2013, p.383). The question may be asked, who performs the right virtuous action – a kind person, an honest person or a just person?

3. As we live in an evolving and ever-changing society, some virtues which may have been acceptable years ago may no longer be regarded as virtues. For instance, paternalism, which was an acceptable virtue of medical doctors decades ago, is no longer regarded as a virtue in the modern Western culture recognising respect for patient autonomy (Hope *et. al.* 2003, p.10).

4. Rachels and Rachels (2012, p.171) also raise the inability of virtues to solve conflict amongst them. It may sometimes be difficult to be honest and kind at the same time, if someone asks your opinion regarding an apparent disastrous new hairstyle.

10.2.1.2 Strengths of virtue ethics

However, virtue ethics definitely have some strengths:

1. It emphasises some aspects of morality, which may not be important in other theories. Some hard or fast rules or acts may be morally acceptable, but virtue elevates it to something more serene.

2. Gardiner (2003, p. 301) argues that virtues are the foundation of morally acceptable behaviour and conduct, from which all other duties and obligations will flow. In other words a virtuous person does not need another moral theory like deontology to guide him; his set of virtues will do so. He also believes that virtue ethics has a number of advantages over the four principles of Beauchamp and Childress. These include the recognition of our emotions as part of our moral perceptions, and also the motivation of the agent for sincerely wanting to do the right thing, and not merely following a set of principles or rules. In other words, it provides a solid basis for moral motivation.

Against this background, I believe that virtue ethics is not an inferior or subordinate theory in comparison to the other major theories. This view is supported by Oakley (2012 p.100):

> It is true to say that virtue ethics does not deliver an "algorithm" of right action (as Aristotle put it), and that a virtue ethics criterion of rightness is perhaps less precisely specifiable and less easily applicable than that given by consequentialist theories (although perhaps not compared to those given by Kantian theories). But it is perhaps an overreaction to argue that this undermines virtue ethics' claim to provide an acceptable approach to ethical justification. For virtue ethicists often give considerable detail about what virtuous agents have done and would do in certain situations, and these details can help us to identify what is right to do in a particular situation. (We might not gain any more precision from the directives of contemporary Kantian and consequentialist theories which advise us to do what a good Kantian or consequentialist agent would do.) And further, virtue ethics need not claim that there is only one true account of what a virtuous person would be and do, for it can allow that, sometimes, whichever of two courses of action one chooses, one would be acting rightly. (my emphasis)

This emphasises one important aspect of virtue ethics. While consequentialist and Kantian theories allow only one action according to the acts, rules and duties, which need to be followed to address a particular moral dilemma, virtue ethics recognises the possibility that the same goal may be reached by the application of different virtues or the execution of different virtuous acts.

10.2.2 **Virtue ethics and medicine**

In his book, Albert Jonsen (1990) discusses the old ethics and those who exemplified those virtues associated with the old ethics. Hippocrates and the principle of non-maleficence, Richard Cabot and his emphasis on competence and the parable of the Good Samaritan and the virtue of compassion all serve as examples of some of those values expected from medical professionals to "serve our lords, the sick". Today, with the pressure from health care funders and other institutions often dictating the way we treat our patients and

infringing on the doctor-patient relationship, it is even more important for medical professionals to build their practice of medicine on an incorruptible and virtuous basis.

The medical profession has not been immune to scandals, including unethical and unprofessional behaviour as well as the exploitation of patients and their suffering. Nevertheless, it is still generally regarded as a virtuous profession, with some virtues seen as an integral requirement of the characteristics of a medical professional. The list of virtues expected from a virtuous healthcare practitioner includes benevolence, compassion, conscientiousness, honesty, justice, etc.. Some of them, like the virtues of benevolence and justice, form the basis of the four principles of biomedical ethics (Beauchamp and Childress 2013, p.381). These authors have also identified five focal virtues which "provide a moral compass for health professionals" (*ibid*., p.37). These five focal virtues include compassion, trustworthiness, integrity, conscientiousness and discernment. This latter virtue, the virtue of discernment, is the bedrock of an ethics of responsibility and will be discussed in more detail below. It represents practical and moral wisdom, prudence and the Aristotelian concept of *phronesis* (Van Niekerk and Nortje 2013, p.30; Pellegrino and Thomasma 1993, p.84).

As no moral or ethical theory, nor any principle, is able to address and solve all possible bio-ethical dilemmas in medicine and life, the correct application of the most appropriate theory or principle in a given circumstance requires insight and practical wisdom to obtain the best possible solution. For instance, in the application of the four principles of biomedical ethics (Beauchamp and Childress 2013), our actual duty is ultimately determined through the processes of balancing and specification. Only practical wisdom enables us to objectively attach a weight to all the different options. It is therefore obvious that the health professional requires practical wisdom to be able to navigate the sometimes stormy waters between the Scylla and Charybdis of bio-ethics and the issues related thereto.

10.2.3 **An ethics of responsibility**

Van Niekerk and Nortje (2013) promote a framework for moral reasoning in bioethics based on an ethics of responsibility. According to them (2013, p.28) "to take or accept

responsibility means to be able to be held accountable for whatever decisions are taken, on the assumption that reason can be provided, that they have been thought through, and even though they might be fallible." We can no longer morally hide behind moral rules, codes or rules, but "it demands that we be accountable for everything we invent and design in our attempts to construct, apply and evaluate our life ethos – i.e. the value system according to which we live." Is an ethics of responsibility not a corollary from the First Aphorism of Hippocrates (as quoted in Jonsen 2006, p.669)?

> Life is short; the medical art is long. Opportunity is fleeting, experience perilous and decision difficult.

Jonsen (2006) discusses the impact of medical technology on therapeutic freedom, and in particular that patients may feel that it is imperative to make use of a specific technology, even though it may be futile. According to him, the application of this aphorism allows for "the reconciliation of technology and therapeutic freedom" in making a clinical decision, "to do something at the right time, for the right reasons, to do so with the awareness of the possibility of failure and error and to take responsibility for the action" (*ibid*. p.672).

I believe that this is exactly what an ethics of responsibility is advocating. Whether it is in deciding what an appropriate treatment option or use of technology might be, or, in keeping with this topic, the management of genetic information.

The ethics of responsibility is based on two principles. First, we must accept that our framework for moral decision-making is not perfect and that it can fail. Secondly, our moral decision-making processes must take into account all important action guides, like moral rules, norms and principles, as well as what we ultimately want to achieve – it is "a knowledge of both means and ends" and the dynamics between these two are such that "the end that we choose will influence the means we adopt to acquire it, and vice versa" (Van Niekerk and Nortje 2013, p.30).

10.2.3.1 The virtue of *phronesis*

According to Hofmann (2002, p.136), many individuals believe that medicine must be viewed as an art (*téchnê*), while others claim it to be a combination of art and science (*episteme)*. There is also a third group who maintain that "the paradigm of medicine is to be found in the concept of practical reasoning (*phronesis)*."

Aristotle used the term *phronesis* for the virtue of practical wisdom, "the capacity for moral insight, the capacity, in a given set of circumstances, to discern what moral choice or course of action is most conducive to the good of the agent or the activity in which the agent is engaged" (Pellegrino and Thomasma 1993, p.84).

The concept of practical wisdom is regarded by Pellegrino and Thomasma as a keystone in medical virtue ethics, forming the "link between the intellectual virtues – those that dispose to truth (science, art, intuitive and theoretical wisdom, etc.) - and those that dispose to good character (temperance, courage, justice, generosity, etc.)" and labelled it "medicine's indispensable virtue" (*ibid.*, p. 84).

Thomas Aquinas used the term prudence, taking into account not only Aristotle's concept of *phronesis*, but also the "supernatural virtues of faith, hope and charity", as well as the moral and intellectual Aristotelian virtues (*ibid.,* p.85). For him, prudence was "a *recta ratio agibilium*, a right way of acting (*op. cit*.), taking both the intellectual aspects of the practice of medicine as well as the moral virtues into account. As already stated, prudence can also be regarded as midpoint between the vice of recklessness and the vice of avoiding danger at all costs (Van Niekerk 2011, p.31).

Prudence, practical wisdom and *phronesis* all depend on the ability of practical reasoning. According to Kinsella (2012, p.35) "*phronesis* emphasises reflection (both deliberative and that revealed through action) as a means to inform wise action, to assist one to navigate the variable contexts of practice, and as directed towards the ends of practical wisdom."

Phronesis is the moral knowledge which enables, us through a process of deliberation, to "synchronise" that what is required by the situation, and that what can be done according to the moral virtues we adhere to. It allows us to find a moral solution for a particular

problem against the universal background of virtue ethics. Van Niekerk and Nortje (*op. cit*.) states: "[I]n this sense, deliberation (the essence of *phronesis*) is a dialectic movement between guides to action and the requirements of the practical situation, as well as the possible consequences of the action".

10.2.3.2 A theory accepting the possibility of failure

It is important to realise that this approach is neither perfect, nor fail-proof – it is an ethics of fallibility (*ibid.,* p29). There will be times when we ultimately realise, often with the benefit of hindsight, that our decision was not the best one. This is permissible, as long as we can justify our decision with objective and scientifically supported arguments. The principle of *diligens paterfamilias*, the reasonable man, has long been accepted as an objective and impartial way to judge a medical practitioner. In this process, the actions of an individual is judged against what his peer group would have done in a similar situation; not against that of a super-specialist working in optimal conditions. One can only assume that the same principle will apply when judging an unintentional wrongful decision by a health professional based on an ethics of responsibility.

10.2.4 Practical application of an ethics of responsibility in genetic dilemmas

With all the possible permutations encountered in medicine, and in genetics, it is impossible for any healthcare practitioner to have all the knowledge, all the time, when confronted with an ethical dilemma.

Virtuosity is most probably the most important requirement for a health care worker to have. If you are not a virtuous person, what will drive you to conform to the rules of your profession? As in the words of Van Niekerk (2011, p.29) "the fundamental assumption of a virtue approach to ethics is that moral status is conferred on acts, not because of some characteristic of the act (as deontology asserts) or because of the consequences of the act (as utilitarianism asserts), but because of the character traits of the actor himself or herself."

In practice, an approach along the lines of an ethics of responsibility is most probably the most practical way to translate ethical theory into practice, especially when superimposed on the principles of biomedical ethics, and in particular the principles of respect for autonomy, beneficence and non-maleficence. In applying the insight offered by the virtue of *phronesis*, the health care practitioner will be able to identify his actual moral duty through the processes of weighing and balancing, and execute it in a responsible manner.

Even if it turns out retrospectively that the decision by the health care practitioner was not necessarily correct or the best available option, an ethics of responsibility accepts that we sometimes may or will fail, even though we may have had the most honourable moral intention. However, as long as we can justify our initial decision and proof that we acted with discernment and only in good faith, failure, although never the preferred end-result, will be permissible.

An ethics of responsibility takes into account not only the rights of the index patient, but also the rights of others, as well as our duty to them. In genetic practice, the importance and potential consequences of a genetic abnormality to the family may be such, that the healthcare practitioner will act irresponsible if he conforms to the index patient's wishes and withhold this information from the family. Based on this moral approach, there is therefore a responsibility on the healthcare practitioner to inform at-risk family members, if he is unsuccessful to obtain the cooperation of the index patient.

Although the decision of the healthcare practitioner to divulge confidential information to others, may on the face of it seems to "harm" the index patient, a virtuous healthcare practitioner will also be the first to extend other virtues, like compassion, to those who may have been "harmed" by his decision.

10.3 A brief review of the other major moral theories and their relevance for this discourse

As stated above, I believe that an ethics of responsibility based on the virtue of *phronesis*, discernment or practical wisdom provides the best moral and ethical platform for the

healthcare worker to operate from when dealing with the thorny issues of medicine, and in this case the ownership of genetic information in particular. Nevertheless, it is always important, at least for the sake of constructive debate and reflection, not to view a particular moral approach in isolation, but also to view it against the background of other moral and ethical theories. In doing so, we can at least compare the different schools of thinking and identify aspects on which these theories may be in agreement or in conflict with one another.

A brief review of three other major moral theories, i.e. utilitarianism, Kantian deontology and the principles of biomedical ethics as defined by Beauchamp and Childress (2013), will confirm that even when viewed from these particular moral viewpoints, a theory based on an ethics of responsibility cannot be criticised or regarded as inappropriate or irrelevant when dealing with issues related to the ownership of genetic information.

10.3.1 **Utilitarian theory**

Utilitarianism is the most prominent consequentialist theory. It accepts only one basic ethical principle, i.e. the principle of utility. The primary aim is to produce the greatest good (or the least possible harm) to the greatest number of individuals in an impartial manner, where everyone is equal and counts the same.

According to the principle of universal utility, “an act is right if it brings about the greatest increase in the world of consequential good of all the alternative actions available, or the least increase in evil consequences of all the alternatives” (Hull 1979, p.2). This is a function of all the consequences, direct or indirect, predictable and unforeseeable. It is impartial, as everyone possibly affected by the act, counts the same weight. This act becomes one’s *prima facie* obligation.

How judgment is reached through the decision making process to determine whether a particular act is of maximum utility or minimum disutility depends on whether an act utilitarian or rule utilitarian approach is followed. In the former the particular situation dictates the decision (act utilitarianism is also sometimes called situation ethics) (Hull 1979).

The rule utilitarian theory appeals to a rule to tell us what to do in a particular situation, and the rule with the greatest net utility then becomes the *prima facie* obligation. It is important to remember that these rules can be revised if we know that a specific rule, like truth-telling, may not have the best consequences in a particular situation. Rachels and Rachels (2012, p. 120) see this move from act to rule utilitarianism as follows: "In shifting emphasis from the justification of acts to the justification of rules, utilitarianism has been brought into line with our intuitive judgments". These rules have to be constantly and indiscriminately obeyed.

Health, like happiness and freedom, is often regarded as an agent neutral or intrinsic good; something each and everyone will value and strive for. I will, for the purpose of this discourse at least, focus on this set of values rather than the hedonistic values of happiness and pleasure as advocated by Jeremy Bentham and John Stuart Mill (Rachels and Rachels 2012, p.110), although it may be argued that a state of physical well-being as a reflection of one's health status will ultimately result in happiness or pleasure.

10.3.1.1 Relevance for this discourse

Utilitarianism plays an important role in public and institutional policy-making. In public health, the aim is primarily based on beneficence- and non-maleficence; either to benefit or to prevent harm to the majority of society, whether this is through vaccinations, notification of disease or even institutionalisation of mentally ill individuals. In this regard, the people to benefit from such a consequence-based policy are usually unknown to the patient who may be the source of an outbreak of disease or potential threat to the society. If it is acceptable to "sacrifice" an individual's privacy and confidentiality for the benefit of the anonymous masses, don't identifiable family members have similar or even more rights to access of important genetic information when it comes to hereditary cancer syndromes and where surveillance or preventative surgery may protect them?

When dealing with genetic information, one is in effect dealing with information which extends beyond the individual sphere. We are also dealing with information reflecting the (possible) genetic status of the family and even society. From a utilitarian perspective, it is

obvious that this information must be applied to the benefit of as many individuals as possible. It may be argued that utilitarianism holds us accountable not only for the execution of a good act (like informing at-risk family members), but also for preventing harm. This is obviously very relevant when dealing with genetic information, as an omission to inform other family members of a potential genetic risk may potentially harm these individuals. The utilitarian will therefore argue that the breach of confidentiality and privacy is completely justifiable, given the positive impact dissemination of this information will have on the family and the community. Genetic information regarding hereditary cancer syndromes is one such example where the benefit to the majority heavily outweighs the (potential) harm to the individual, using health and prevention of disease as the calculus. Having said this, this approach obviously infringes on the right to confidentiality and privacy of the index patient by supporting the "tyranny of the majority" (Rachels and Rachels 2012, p.115).

Is the latter situation justifiable from a utilitarian perspective? Applying health and the prevention of disease as the calculus of utility, it seems as if there can be no moral objection to veto someone's refusal to divulge this type of information as long as all reasonable steps are taken to protect the privacy of the family as a whole.

10.3.2 **Kantian deontology**

Deontological theories (from the Greek *deon*, meaning duty) are based on the principle that one must choose your actions according to standards of duty or obligation that refer not to the consequences, but to the nature of the action. These theories are also called duty-based moral theories. Hull (1979, p.4) states that deontologists are often also absolutists, "but some deontologists do hold that what is morally right in a given situation may differ from what is morally right in any other given situation".

A central theme in the argument of deontologists is the fact that consequences do not count; a morally wrong act may have entirely good consequences, but it is not permitted. Along the same line, a morally right act may have entirely bad consequences, but still needs

to be executed. For consequentialists “good is right”, while deontologists hold that “right is good”.

A distinction is also made between act and rule deontologists, and the best-known rule deontology theories include religious rule deontology and Immanuel Kant’s rational rule deontology (Hull 1979). This “rule morality” may either confer a positive duty (what we must do) or a negative duty (what me must refrain from doing).

Kant formulated two types of imperatives, i.e. the hypothetical and categorical imperatives. The former is conditional and non-compulsory, and merely indicates what an individual must do in order to achieve a specific end-result or goal. A categorical imperative defines an unconditional command or rule that has to be executed.

Kant (1964) as cited by Van Niekerk (2011, p.26) formulated two versions of the categorical imperative:

a) “Act only on that maxim through which you can at the same time will that it should become a universal law”, and
b) “Act in such a way that you always treat humanity, whether in your own person or in the person of any other, never simply as a means, but always at the same time as an end.”

10.3.2.1 Relevance for this discourse

When applying Kant’s two categorical imperatives to this discourse, it does appear as if these imperatives may be in conflict with one another.

The first formulation of the categorical imperative has as its basis the principle that whichever rule or maxim an individual decides to apply to a particular situation or dilemma, must be the same rule he or she would desire everyone else also ought to apply in a similar situation. In very simple terms, it is almost a matter of “what is good for the goose, is good for the gander”.

I believe the first formulation of the categorical imperative speaks to the sharing of genetic information amongst family members. If an individual states that he himself would prefer to be informed of any possible genetic risks, which his or her family may harbour, one can then assume that he will offer that same information to other family members at risk if he was to be the index patient. In executing this maxim, the family will then all subscribe to the concept of a joint account as defined by Parker and Lucassen (2004). According to them, the shared genetic material amongst family members must be viewed as a "joint" account rather than a "personal" account. By doing so, the knowledge of a hereditary cancer syndrome and the duty to share that information with family members will become "universalised" at least amongst the family members, to the effect that this information will be available to all family members. This is presumably the position any member of a family, even the index patient if he were not in the specific position of being the first member of a family to be diagnosed with a hereditary cancer syndrome, would prefer to be in if another of his family served to be the index patient.

The second formulation appears to promote the opposite argument. By divulging confidential genetic information against the wishes of the patient, and with the primary aim to benefit other at-risk family members, it may well be argued that we are only treating the index patient as a means to benefit others and not as an end in himself. From a scientific perspective, hereditary cancer syndromes tend to blur the concepts of "a means" and "an end". The index patient may have already manifested some of the genetic abnormalities on a clinical level. He has already been diagnosed with cancer and knowledge of his genetic status may be of little further value to him. (There are exceptions as already alluded to. In some syndromes, like Lynch syndrome, patients may be at risk for the development of metachronous tumours, and surveillance of the other organs at risk is indicated.) He has gained maximum information and subsequent benefit from the identification of the genetic abnormality. I do not believe that divulging that information to family members at-risk, is treating the index patient as a means to their end, as that information already served him as an end in himself.

One of the problems with Kantian theory is the overemphasis it places on duty, while at the same time it underemphasises special relationships, like that between different family members (Beauchamp and Childress 2013, p.366). In practice, this theory requires us to

uphold the rules and duties in all circumstances. This may result in a conflict of duties – a typical problem of Kantianism - and require us to lie to the family member of a newly diagnosed hereditary cancer patient if we are specifically asked whether he or she may be at risk or not, and we do not have the consent of the index patient to divulge that information. The motive of duty is so overwhelming, that the deontologist often lacks sympathy, compassion and the other humane attributes so important in the practice of medicine. Withholding this important information is in conflict with a utilitarian approach where we seek to do good or prevent harm to the greatest number of people, in this case the patient and his or her offspring.

10.3.3 **The principles of biomedical ethics**

Beauchamp and Childress (2013) developed a model for biomedical ethical deliberation based on four principles, i.e. respect for autonomy, beneficence, non-maleficence and justice. Since its first publication in 1979 and spanning seven editions, *Principles of biomedical ethics* has become an important textbook and source of information and guidance for many health care workers, or, for that matter, anyone confronted with bioethical issues. DeGrazia (2003, p.219) believes that it would be difficult "to find a text that has been more influential and more frequently cited". He also commends the authors for their willingness to implement change, and regards it as one of the book's strengths.

The book, sometimes negatively referred to as the Georgetown mantra or "principlism" as it tends to imply that those "chanting" the four principles may see themselves as bio-ethicists although they may lack any formal training, has also drawn more than its fair share of criticism through the years (DeGrazia 2003, p.220), with Bernard Gert, H Danner Glouser and Charles Culver the most unsparing critics (Beauchamp and Childress 2013). The fact that the four principles lack the support of an overarching ethical theory has always been criticised. In the first three editions there was some reference to ethical theories which could support these principles. Beauchamp and Childress, despite their preference for rule-utilitarianism and rule-deontology respectively, were from the beginning pluralistic in their approach to identify a moral foundation to base the principles on (DeGrazia 2003). In the

fifth edition the idea of a common morality was embodied as the ultimate source of moral principles and norms.

The concept of a common morality forms an integral component of the four principles approach. Beauchamp and Childress (2013, p.3 and p.417) define the common morality as "the set of universal norms shared by all persons committed to morality". Gillon (1995, p.323), a fierce supporter of the four principles approach, states that "it seems to cut across national, cultural, religious, political and philosophical divisions and to provide a common set of *prima facie* moral commitments, a common moral language and a common moral-analytic framework for biomedical ethics."

Beauchamp and Childress promote an integrated model, which is based on considered judgments and reflective equilibrium. In this model, there is a constant flow of information between principles and rules at the top and cases below, through a bidirectional inductive and deductive flow. The considered judgments are those most "pure", undistorted and unbiased judgements in which we do experience no problem to decide what is "right" and "wrong". These reflect the common morality. These considered judgments are the fixed points on our moral compass. The second component of this model is the application of John Rawls' "reflective equilibrium" to "match, prune and adjust considered judgments, their specifications and other beliefs to render them coherent." (Beauchamp and Childress 2013, p.405). This process is by the nature of it, a continuing process in search of coherence, where we constantly align our moral theory with the considered judgment or *vice versa*, whenever conflict arises. This process assists us to use a process of specification to apply the principles in a particular situation, to formulate a set of the most appropriate principles and rules to solve a particular dilemma. By going through this process, we are thus able to identify our actual duty from the set of *prima facie* duties.

According to Childress (2012, p.67) "a principle-based approach must, as a minimum, hold that some general norms or action guides are central in moral reasoning". Although principles and rules both define norms, the former are of a more general nature, while rules tend to be more specific. Principles are therefore more content-thin while rules tend to be specific and content-rich. The formulation of a rule out of a specific principle is a progressive process in which the concept is refined – this process is called specification. "Principles often

provide warrants for more specific rules, while rules specify more concretely the type of prohibited, required, or permitted action" (Childress 2012, p.67). Beauchamp (2003, p.269) states the following regarding specification:

> "Secondly, these abstract principles need to be specified to make them suitable for the analysis of a context, case, or policy. *Specification* is a process of reducing the indeterminateness of general norms to give them increased action guiding capacity, while retaining the moral commitments in the original norm. Filling out the commitments of the norms with which one starts, is accomplished by narrowing the scope of the norms."

W.D. Ross developed the concept of *prima facie* duties. According to Beauchamp *et. al.* (2008, p. 27):

> "A *prima facie* duty is a duty that is always to be acted upon unless it conflicts on a particular occasion with an equal or stronger duty. A *prima facie* duty, then, is always right and binding, all other things being equal; it is conditional on not being overridden or outweighed by competing moral demands."

The four principles are equal in standing without moral priority of one over the others. They are all *prima facie* duties and when in conflict with one another the actual duty must be determined through the processes of weighing and balancing. These processes are not only dictated to some extent by the common morality, but the final action (or lack of it) must also fall within the ethical and moral borders as defined by the common morality.

10.3.3.1 Relevance for this discourse

Three of the principles, respect for autonomy, beneficence and non-maleficence, are central to this discourse.

The principle of respect for autonomy can be stated as a negative or positive obligation (Beauchamp and Childress 2013, p.107). The negative obligation requires "that autonomous actions not to be subjected to controlling constraints by others". Exceptions may exist, and

these valid exceptions are incorporated through a process of specification. The positive obligation "requires both respectful treatment in disclosing information, and actions that foster autonomous decision-making" (*op. cit*.). Obligations created by the principle of autonomy are (1) informed consent, (2) confidentiality, (3) truth telling and (4) effective communication.

The principle of nonmaleficence imposes an obligation not to inflict harm on others. In medical ethics it is closely associated with the maxim *primum non nocere*, or "above all [or first] do no harm" (Beauchamp and Childress 2013, p.151). Nonmaleficence requires intentionally refraining from actions that cause harm, while beneficence is based on positive actions. Generally, obligations of nonmaleficence are more stringent than obligations of beneficence, and, in some cases, nonmaleficence overrides beneficence (*op. cit*.).

A beneficial action does not necessarily take second place to an act of avoiding harm (*ibid.,* p.152). There is no rule in ethics which favours avoiding harm over providing benefit; one clinical example is weighing up the risks and benefits of oncotherapy in treating cancer. In the context of genetic information, maintaining and respecting confidentiality and privacy are not absolute rights or duties. If the index patient refuses that this information is disseminated, and it is known that access to this information will be beneficial to other family members, then the benefits (to the family) outweigh the harm it may cause (to the index patient). Our actual duty will then be to act benevolent to the at-risk family, although there will be disrespect for the index patient's autonomy. Except for the loss of confidentiality and privacy, this act will result in no other harm or maleficence to the index patient; in fact, it will save the family from the latter.

11 Conclusion

The scope of medicine, like any other scientific field, is constantly changing due to the development of new technology, which not only improves our diagnostic ability and accuracy, but also our ability to predict the risk for the development of a disease and its prognosis. Although these changes give us a far better understanding of the science we practise, it often also raises its own unique moral and ethical issues. Like any other scientific discipline, it is important that new technology, knowledge and information be applied (as far as possible) to the benefit of not only the human species, but also to the benefit of other species, our environment, our world and universe. If not, we always stand the risk of abusing this newly acquired scientific ability and skills to the detriment of ourselves and one another. A state of technological chaos and disorder, very similar to the "state of nature" as formulated by Thomas Hobbes, and also often portrayed in science fiction movies, will evolve. In this state, and in the context of this thesis, the abuse of genetic information will become yet another weapon to inflict damage to ourselves and others.

Molecular pathology, including genetics, is at present one of the fastest developing pathology disciplines, changing the way we practice all other medical disciplines, including histopathology, haematology, and microbiology. It is the duty of philosophers and bio-ethicists to assist science in implementing new scientific developments in a responsible, and morally and ethically acceptable manner. This includes developing moral and ethical principles regarding the management of genetic information, to ensure its optimal use and application to the benefit of all interested parties.

Let us first look at the future prospects of genetic medicine as such, and finally conclude with a few comments on the main issues discussed in this document.

The practice of medicine is moving more and more into the scope of so-called P4 medicine. The convergence of systems biology, the digital revolution and consumer-driven healthcare is transforming medicine from its current predominantly reactive mode, which is focused on treating disease, to "a pro-active P4 medicine that is predictive, preventive, personalized and participatory" (Hood and Flores 2012, p.614).

Urban (2015, p.547) believes that precision medicine, similar to the above P4 system, will be the paradigm for medicine in future. This will define an individual's illness on a genetic and biochemical level. He believes it will have far-reaching effects, including changing the *International Classification of Disease (ICD)* coding system, the use of health records and even health care funding.

Technical advances in the analysis of genetic information through modern techniques like next generation sequencing supported by unlimited information technology systems will be the basis for this new way we practise medicine, or more importantly, how the public manages their own health and all data pertaining to it. In future, the amount of health information flowing between patient, health care practitioner, health care provider and other interested third parties will be vast. It may be very difficult, if not impossible, to police the maintenance of confidentiality and privacy of information, including genetic information.

At the same time, we are starting to view disease, and even social behaviour, from a less discriminative perspective. We accept the science behind psychological disturbances, even to its genetic level. The concept of disease has lost its stigma; people with neurological debilitating diseases like Parkinson's disease or post-stroke conditions are now part of public life. Thirty years ago, it was almost a social taboo for someone with debilitating diseases to openly socialise in public. The same applies to oncotherapy; cancer patients no longer hide in shame, but use their alopecic heads as a strong message to campaign for the prevention and screening of cancer.

We have only traversed the proverbial peak of the iceberg related to genetic information. Some other issues, central as well as more peripheral to this debate, were not discussed in any detail. These include issues surrounding adult-onset diseases and the rights of children, as well as the rights of future, still to be born, generations. There are many other issues which are just as important, including direct to consumer (DTC) testing, the performance of testing on "vulnerable" individuals (like prisoners and the mentally ill), etc. Research done on genetics, including biobanking, is a topic which by its comprehensive nature justifies a discussion of its own, and will not be dealt with in any detail. Some of the problems unique to this field of medicine are the further management of incidental findings discovered in the

genome of individuals during research. These are so-called "variants of unknown significance" (Urban 2015, p.545). This is problematic as the exact risk harboured by these abnormalities cannot be predicted or has not yet been quantified. A word, which has also appeared in the genetic vocabulary, is the so-called "incidentalome"[17] This "incidentalome" debate is now central in the discussion of the right to know or not to know in relation to biobank research (Chadwick *et. al.* 2014, p.55).

In this thesis only two issues were discussed. First, it is obvious that the concepts of phenotype and genotype can no longer be viewed as two completely separate entities. They have merged, and to such an extent, that is more practical to view them as a unified concept. Therefore, we need to change the way we obtain consent for surgical procedures and histopathology examinations. The consent must be comprehensive and all-inclusive, and must include the genetic analysis for both somatic and germline mutations. This will enable the histopathologist to conduct a comprehensive analysis of the specimen. Not only will this enable the pathologist to comment on the susceptibility of the tumour to treatment as well as the prognosis of the patient, but it will also allow for the diagnosis of hereditary cancer syndromes. In addition, I foresee that the inclusion of genetic information as part of the histopathology diagnosis will become the norm in the future, as will soon be the case with nervous system tumours (Louis *et. al.* 2014).

Secondly, I have discussed the legal and moral/ethical ramifications regarding the dissemination of information regarding the presence of a hereditary cancer syndrome. From a legal perspective, I do believe that refusal by the index patient to inform at-risk family members, does allow the further dissemination of such information, on condition that the index patient is informed and offered the opportunity to cooperate. This position is also supported by the professional guidelines in South Africa as well as elsewhere.

From an ethical and moral perspective, I believe that the bio-ethical dilemmas encountered in modern medicine, including the issue regarding genetic information, can best be solved along the lines of an ethics of responsibility. In this virtue-based theory, the virtue of *phronesis* or practical wisdom is the guiding factor. Although we may sometimes be wrong

[17] Incidental and unexpected findings in clinical medicine are a well-known phenomenon. In radiology something unexpected may be noted on an image, and sometimes the clinical significance of this incidental finding, refer to as an incidentalome, may be unknown.

in our bio-ethical decisions, it will not fault us as long as we can justify our good intentions and actions made based on practical wisdom applied to a specific scenario.

I believe that none of the other major moral and ethical theories is in conflict with this approach. The utilitarian strives to use this information to do good or prevent harm to the greatest number (i.e. the family). The deontologist bases his argument on the first categorical imperative, that we must do to others, what we would like others to do to us in a similar situation, i.e. by sharing information which may be of benefit. The actual duty of the principlist to inform the at-risk family members is formulated by weighing up respect for autonomy of the index patient with the beneficence to the family and the harm (maleficence) it may cause to both the index patient and the family.

The ultimate value of genetic information is in its benefit to us all. Let us start to "desensitise" the moral issues around the confidentiality and privacy pertaining to genetic information; let us start to use that vast knowledge and information obtain from genetic testing in a responsible and fair manner to the benefit of all – the index patient, the family and ultimately humankind.

Genetic information regarding a hereditary cancer syndrome does offer us the chance to make a difference in the life of others.

12 Annexure A

Lynch Syndrome

Lynch syndrome (LS) (Vogelzang 2013) is a syndrome with an autosomal dominant inheritance pattern, characterised by an earlier age of development for colorectal carcinoma as well as a higher risk for other cancers. It was previously called hereditary nonpolyposis colorectal carcinoma (HNPCC), but as there is a risk for cancers other than colorectal carcinoma, the preferred terminology is now Lynch Syndrome.

Approximately 3% of colorectal carcinomas are caused by LS. These carcinomas typically occur at an earlier average age than in the general population (45 years versus 63 years) and most (70-85%) are proximal to the splenic flexure, therefore having a right-sided predilection. These tumours show an accelerated carcinogenesis with small polyps transforming within 2 to 3 years into carcinomas. In addition, there is a high risk of 25 – 30% for the development of either synchronous or metachronous colorectal carcinomas.

There is an increased risk for malignancy at extracolonic sites:

- endometrium (40 – 60% lifetime risk for female carriers);
- ovary (12 – 15% lifetime risk for female carriers);
- stomach;
- small bowel;
- hepatopancreaticobiliary system;
- upper uro-genital tract, like transitional cell carcinoma of the renal pelvis;
- prostate (although this is controversial);
- breast;
- adrenal cortex;
- brains (glioblastoma); and
- skin tumours, like sebaceous adenoma and carcinoma and multiple keratoacanthomas in the Muir-Torre variant of LS.

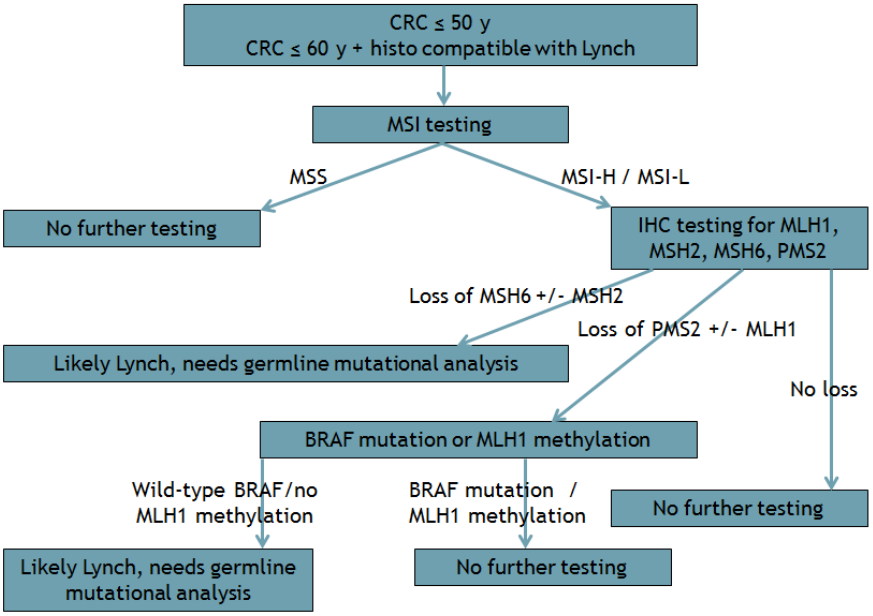
These tumours tend to be often poorly differentiated with mucinous and signet-ring cell features, a Crohn's-like reaction and intra-epithelial lymphocytes. The survival rate for colorectal carcinoma is higher.

There are sets of criteria (Bethesda and Amsterdam) which can be used by clinicians to determine the risk for an individual to suffer from LS.

The diagnosis depends on the demonstration of a germline mutation in a mismatch repair (MMR) gene. These genes are *MLH1, MSH2, MSH6* and *PMS2*, although for completeness the *EPCAM* gene is also sometimes included (although it is strictly speaking not a MMR gene, but causes *MSH2* inactivation). A loss of MMR genes result in the accumulation of defective microsatellites, leading to microsatellite instability (MSI) which puts the patient at risk for the development of cancer due to the potential accumulation of genetic defective material.

In normal practice, based on the clinical history and the morphological findings, the histopathologist will consider the possibility of LS. Immunohistochemistry (IHC) can then be performed to demonstrate loss of one or more of the MMR genes. Alternatively microsatellite stability status can be tested for, and classified as low (MSI-Low) or high (MSI-High). However, this is not diagnostic for LS, as loss of MLH1 may for instance also be due to hypermethylisation[18]. Therefore, genetic testing has to be performed for confirmation of the genetic disease. The ethical issue is when consent for genetic testing is required; is it required for immunohistochemistry or MSI testing, or only for genetic testing itself. There are two schools of thought. The one believes it is only required for the genetic testing as such, whilst the other believes it is even required for the immunohistochemistry and MSI testing as it is a form of genetic screening (Chubak et al 2011; EGAPP Working Group 2011; Williams & Williams 2011).

[18] DNA methylation is one of the two main epigenetic mechanisms, the other mechanism being histone modification (Griffith and Stotz 2013, p. 116).



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