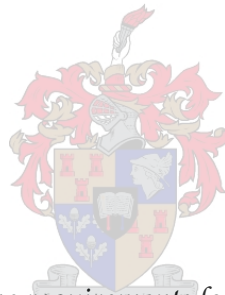


# Ethical dilemmas in Gaucher disease

by

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A thesis, like a painting, constructs an image of its creator – the painting with visual images, the thesis with ideas.

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## ABSTRACT

Gaucher disease (GD) is a rare and chronic, genetic disorder which presents immensely challenging ethical dilemmas for patients and families. Important is the high-cost, high-benefit, but low volume treatment for Gaucher disease, which creates incessant resource allocation dilemmas for healthcare professionals and policy makers and lack of access to care for patients. Apart from expenditure, Gaucher disease provokes numerous other ethical dilemmas including genetic screening, disclosure of genetic information and abortion. These issues pose important social and ethical challenges to the discipline of biomedical ethics. This study seeks to interrogate some of these burning ethical dilemmas. By means of a fictional biomedical ethics case report which deals with a pregnant patient subsequently diagnosed with the rare Gaucher disease, it simulates and highlights some of the numerous ethical dilemmas that a pregnant Type 1 Gaucher disease patient may have to ultimately contend with. This study will attempt to illuminate ideas of ring fencing resources for patients with rare or orphan diseases in a resource restricted developing country like South Africa. It will also attempt to provide some guidance when dealing with some of the other burning ethical issues related to Gaucher disease, which includes genetic screening, disclosure of genetic information and abortion.

## OPSOMMING

Gaucher siekte (GS) is a seldsame en kroniese genetiese siektetoestand wat uiters uitdagende etiese dilemmas vir pasiënte en hul families kan veroorsaak. Van besondere belang vir pasiënte, lede van die mediese professie, sowel as beleidskeppers, is die hoë koste, hoë voordeel, maar lae volume behandeling vir Gaucher siekte wat onvermydelike dilemmas veral met betrekking tot veral die toekenning van finansiële hulpbronne kan veroorsaak. Bo-en-behalwe dié uitgawes, ontketen Gaucher siekte verskeie ander etiese dilemmas, insluitend genetiese- toetsing en skandering, die bekendmaking van genetiese inligting, asook aborsie. Hierdie dilemmas kan belangrike sosiale en etiese uitdagings vir die vakgebied biomediese etiek teweegbring. Die tesis ondersoek sommige van die mees algemene etiese dilemmas. Deur middel van 'n fiktiewe biomediese en etiese gevallestudie met betrekking tot 'n swanger pasiënt gediagnoseer met die seldsame Gaucher siekte, word verskeie etiese dilemmas, waarmee 'n swanger pasiënt, wat gediagnoseer is met tipe 1 Gaucher siekte, moontlik gekonfronteer kan word, aangeraak. Hierdie studie poog om, veral in 'n ontwikkelende land soos Suid-Afrika met beperkte hulpbronne, nuwe idees uit te lig wat moontlik finansiële bronne beskikbaar kan stel vir pasiënte met seldsame of wees siektetoestande. Die studie sal ook poog om verdere riglyne te verskaf aangaande ander kwellende etiese dilemmas wat moontlik mag gepaardgaan met Gaucher siekte soos genetiese toetsing, die bekendmaking van genetiese inligting, asook aborsie.

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# Chapter 1

## Gaucher disease literature review

*“Nothing important comes with Instructions.” – James Richardson, “Vectors 3.0”*

### 1. Introduction

“Gaucher disease, a rare”, chronic, “genetic disease” (Hughes D. , 2015, p. 584) poses thought-provoking ethical dilemmas, both for patients and families. Of special significance is the resource allocation dilemma for patients and policy makers due to the high cost of treatment in the context of limited resources. Apart from expenditure, Gaucher disease provokes various other ethical dilemmas for healthcare professionals and patients regarding genetic screening, disclosure of genetic information and abortion (Gross, 2002). Chapter 1 defines a rare disease and presents a Gaucher disease case study, as an example of a rare disease. This will be followed by background information regarding Gaucher disease and will include aspects regarding diagnosis, disease severity, mortality and morbidity, and physical, physiological, as well as social consequences. Subsequently, some of the ethical dilemmas associated with Gaucher disease such as genetic screening and resource allocation are described and explored in more detail.

### 2. Definitions of a rare disease

“There are an estimated 6 000 to 8 000 rare diseases” (De Vruet R. , 2014, p. 4). Most rare diseases “are of genetic origin and affect children at a very early age” (De Vruet R. , 2014, p. 4). Gaucher disease belongs to such a cluster of rare diseases (De Vruet R. , 2013, pp. 6.19-5) (Tambuyzer, 2010, p. 921). The definition of what constitutes as a rare disease vary between continents (Rosenberg-Yunger, 2011). The USA defines a rare disease or condition as “affecting fewer than 200 000 patients (6,4 per 10 000 inhabitants)” (Drummond, 2014, p. 335) while the European Union defines it as “a prevalence of 5 per 10 000 or lower” (Drummond, 2014, p. 335) and the United Kingdom (UK) a prevalence of less than 1 in 50 000 per population (Drummond, 2014, p. 335) (Dani, 2013, p. 220).



According to the World Health Organisation, the prevalence lies somewhere between 6,5 and 10 patients in 10 000 (Aronson, 2006, p. 243). It is estimated that “one person out of 15 could be affected by a rare disease” globally, which “represents 400 million people worldwide of which 30 million are Europeans and 25 million Americans” (De Vruh R. , 2013, pp. 6.19-5). However, rare diseases affect people globally and therefore represent a true global health issue. Rare diseases are sometimes referred to as “health orphans”, because insufficient evidence exists about their origins and “effective therapies are limited” (Remuzzi, 2008, p. 1978) (Tambuyzer, 2010, p. 921).

Living with a rare disease is challenging, as there is often limited treatment, or the disease may be poorly understood by both researchers and clinicians, as well as by family members and the broader community (Kesselheim, 2015, p. 75). Patients with rare diseases often have difficulties in finding expert medical care, which may lead to “a sense of isolation” (Field, 2010, p. 69) and “lack of support” (Field, 2010, p. 69) (Kesselheim, 2015, p. 76). The “financial and social burdens they bear, combined with the limited availability of treatments” (Field, 2010, p. 69) “converge creating a willingness to accept risks in their care in the hopes of finding a benefit” (Kesselheim, 2015, p. 76).

Medicines indicated for these life-threatening or seriously debilitating diseases, are also aptly called ‘orphan drugs’ due to the high costs of medicine development, the rarity of diseases and uncertain benefit (Dani, 2013, p. 221). In the US, 400 of these products have made it to the market (Paulden, 2015, p. 255), (De Vruh R. , 2014, p. 1) (Tambuyzer, 2010, p. 921) (Divino, 2016, p. 1) (Da Silva, 2015, p. 500) (Gong, 2016, p. 4). The Orphanet Drug Report (October 2015: 5), demonstrates that “the number of US orphan medicine designations increased by 12% to 291 in 2014 and rose an incredible 62% to 201 in 2014 in Europe” (Hadjivalisou, 2015, p. 5). Similarly, Hanna et al reported a considerable increase in the cumulative total of marketing authorisations in the EU from 1995 to 2015 for medicines intended for the treatment of rare diseases (Hanna, 2016, p. 113).

Even though these treatments have made a huge difference to patient’s lives, “expense is a large consideration in the treatment” (Wang, 2011, p. 459) of rare diseases, especially since medicine expenses can become rapidly exhausted because health insurance may be limited to a maximum amount covered in a lifetime (Wang, 2011, p. 459) with most of the available therapies (Wang, 2011, p. 459) (Menon, 2015, p. 117).

### 3. A case study

The following discussion is a fictional biomedical ethics case report:

Mrs. X is a 28-year old black female patient, who consulted the nurse at a rural clinic for a slight fever, weakness and pallor coinciding with a swollen stomach and suspected pregnancy. Over the past few years she had recurrent episodes of fever and respiratory infections. She had received unspecified medications for the recurrent respiratory tract infections. She had also visited traditional healers on quite a few occasions.

Mrs. X suffers from chronic bone pain, sometimes excruciatingly intense. When the patient cuts herself, she bleeds quite profusely, and also has unexpected severe nose bleeds. The patient has had two miscarriages in the last 3 years. She was referred to the Steve Biko Tertiary Hospital where they conducted an ultrasound which confirmed that she was 12 weeks pregnant. She also presented with a grossly enlarged spleen (splenomegaly) and an enlarged liver (hepatomegaly) to 3 cm below the costal margin. Concerned with the protruded abdomen, the investigating physician decided to investigate alternate reasons for the enlarged spleen and liver. Malaria was suspected but ruled out through appropriate blood tests.

To evaluate massive splenomegaly, bone marrow aspiration was performed which revealed Gaucher cells in a background of normal erythroid, myeloid and megakaryocytic lineage cells. Bone marrow tests showed marked hyper cellular marrow, diffuse sheets of abnormal infiltrate comprised of macrophages with profuse pale staining cytoplasm with a texture of crushed paper/silk, suggestive of inherited lysosomal storage disease. A dried blood spot (DBS) test demonstrated low activity of beta-glucosidase (36 pmol/spot with reference value of 200-2 000 pmol/spot), which was very low.

According to Li et al, an enzyme blood spot test is a reliable, fast and simple, inexpensive and minimally invasive way of testing for Gaucher disease (Li, 2010, p. 49).

Other diagnostic procedures conducted on the patient included the following: Full blood count which revealed low red blood cell counts and low platelet counts. Quality of life assessments indicated that the patient was suffering from considerable fatigue. X-rays revealed osteopenia and a DEXA assessment further revealed low bone density.

Mrs. X was subsequently diagnosed as a *Gaucher disease type 1* patient. Tragically, despite the fact that the patient visited clinics and hospitals habitually for bone pain, and also pallor (which could have been tested by means of full blood count (FBC)), as well as numerous respiratory tract infections, she was never fully investigated for Gaucher disease. According to Mistry et al, delayed diagnosis after onset of symptoms prevents nearly one in four patients timely access to therapy (Mistry, 2011, p. 110).

In an ideal world, regular ongoing tests should be conducted at diagnosis and then at regular intervals thereafter. However, due to cost and other constraints, many patients do not receive regular ongoing check-ups, which might assist in assessing the patient's progress or deterioration.

The following comprises of a literature review relevant to Type 1 Gaucher disease.

## **4. What is Gaucher Disease?**

### **4.1 Background**

“Gaucher disease is the most common lysosomal storage disorder” (Wang, 2011, p. 464) and is classified as a rare disease (Bhengu, 2011, p. 697). Gaucher disease is divided into three different clinical types, of which type 1 is the “most common” (Cassinerio, 2014, p. 118), while type 3 and type 2 comprise of 5% and 1%, respectively (Bhengu, 2011, p. 697) (Di Rocco, 2014, p. 1905). “In the early 1990's, Gaucher disease was the first of the lysosomal storage disorders that could be treated successfully with enzyme replacement therapy” (De Fost, 2006, p. 830).

“Philippe Charles Ernest Gaucher described Gaucher disease in 1882” (Packman, 2010, p. 2002). Gaucher annotated this disorder, which led to the death of a “32-year old woman” (Baris, 2014, p. 73) that presented with massive hepatosplenomegaly, abnormal histiocytes and cachexia (Grabowski, 2014, p. 10). Gaucher diagnosed a splenic neoplasm in his patient (Mistry, 2015, p. S6). Often at the time of diagnosis, Gaucher disease is easily confused with a malignancy (Mistry, 2015, p. S6).

Following this particular case, “no further reports emerged until 1895 when sporadic case reports of similar patients began” (Mistry, 2015, p. S7) to surface (Mandelbaum, 1912, p. 797). “Mandelbaum, a physician from New York” (Mistry, 2007, p. S7), named the disease “Gaucher disease” and further “expanded the description of the morphologic pathology and anatomy of the disease” (Mistry, 2015, p. S7).

Type 1 Gaucher disease affects “45 000-60 000 people” (Weinreb N. , 2012, p. 3) globally in the general population, but prevalence is seemingly higher with about 1 in 500 to 800 Ashkenazi Jews affected (Weinreb N. , 2012, p. 3). “Approximately 1 in every 12 to 15 people of Ashkenazi descent are carriers of Type 1 Gaucher disease” (Gauchercare, 2016). Morar et al estimated the disease “frequency of Gaucher disease in the Ashkenazim of South Africa” (Morar, 1996, p. 78) to be approximately 1 in 20 (Morar, 1996, p. 78). Gaucher Type 1 disease “represents around 90% of all cases of Gaucher disease” (Weinreb N. , 2012, p. 3) “with an estimated prevalence of 1/40 000 in the general population” (Wang, 2011, p. 464) (Scriver, 2006, p. 12).

In South Africa, “Gaucher disease has been demonstrated to occur in all ethnic groups” (Bhengu, 2011, p. 697). Various studies have also reported occurrence in both South African Afrikaans-speaking Caucasians, as well as in the South African Black population (Morar, 1996, p. 78) (Arndt, 2009, p. 129) (Goldblatt, 1979, p. 209) (Patel, 1984, p. 343). Arndt et al noted that “only type 1” (Arndt, 2009, p. 132) Gaucher disease “has been reported in black South Africans” (Arndt, 2009, p. 132), and they have different gene mutations, while the disease is also clinically severe (Arndt, 2009, p. 129). Most of these patients “presented with severe hepatosplenomegaly and a combination of anaemia, cytopenia and leucopenia” (Arndt, 2009, p. 129).

The previously discussed case study, dealing with a pregnant patient subsequently diagnosed with the rare Gaucher disease, aptly demonstrated some of the ethical dilemmas that a pregnant Type 1 Gaucher disease patient might have to contend with, such as autonomy of the mother on the one hand versus justification for selective abortion on medical grounds and determining the morality of this practice on the other hand.

## 4.2 Definition

Gaucher disease refers to a “rare autosomal recessive” (Di Rocco, 2014, p. 1905) congenital “genetic deficiency of the lysosomal enzyme  $\beta$ -glucocerebrosidase” (Di Rocco, 2014, p. 1905). This disorder impairs storage of glucocerebroside and other glycolipids in various tissues leading to injury of “several organ systems” (Di Rocco, 2014, p. 1905) (Patel, 1984, p. 343).

According to Arndt et al, “type 1 Gaucher disease” (Arndt, 2009, p. 129) is most commonly triggered by an alteration in “the *GBA* gene (localized to 1q21) that codes for the lysosomal enzyme, glucocerebrosidase” (Arndt, 2009, p. 129) (Bhengu, 2011, p. 697).

Rosenbaum et al mention that “the course of Type 1 Gaucher disease is” (Rosenbaum, 2015, p. S49) typically diverse with wide-ranging clinical manifestations and numerous different stages of disease severity (Rosenbaum, 2015, p. 549). This “clinical heterogeneity which marks Gaucher disease is partially attributable to the more than 100 mutations within the glucocerebrosidase gene” (Elstein, 1998, p. 179). “The deficiency in glucocerebrosidase leads to the accumulation of glucosylceramides (or beta-glucocerebrosidase) deposits in the cells of the reticuloendothelial system of the liver, of the spleen and the bone marrow (Gaucher cells)” (Rosenbaum, 2015, p. S49). In Gaucher “types 2 and 3, pathology also occurs within the brain” (Bhengu, 2011, p. 3) (Wang, 2011, p. 464).

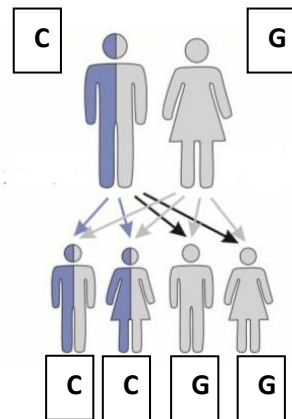
## 4.3 Genetics

The transmission of Gaucher disease is “autosomal recessive” (Di Rocco, 2014, p. 1905) (Bhengu, 2011, p. 698). This implies that both parents of an affected person are carriers of a mutated acid  $\beta$ -glucosidase gene. Thus, “a person develops Type 1 Gaucher disease if he or she inherits two defective copies of this gene (one from each parent)” (Gauchercare, 2016).

“If a person only inherits one defective copy, he or she will not develop Type 1 Gaucher disease, but is considered a ‘carrier’.” A carrier can pass the defective gene to his or her children. With each pregnancy, each carrier has a 50% chance of passing on the defective gene. If both parents are carriers, there is a 25% chance their child will inherit two defective copies and will develop Type 1 Gaucher disease” (Gauchercare, 2016).

**Figure 1.1: Inheriting Gaucher disease (adapted from [http://www.cerezyme.com/patients/gaucher\\_disease.aspx](http://www.cerezyme.com/patients/gaucher_disease.aspx))**

Inheritance of Gaucher disease:



**Legend:**



G=Gaucher disease



C=Carrier (of Gaucher disease)

The chart (figure 1.1) shows how a patient with Gaucher disease when procreating with a carrier, has “a 50% chance of passing on the disease” (Gauchercare, 2016).

## 4.4 Diagnosis

Diagnosis of rare diseases remains a challenge and many patients visit an average of 7,5 physicians before receiving a definitive diagnosis. Even in the best possible circumstances, a percentage of patients will remain undiagnosed (Honey, 2016).

A patient with Gaucher disease, which is progressive and chronic, often remains undiagnosed (Mistry, 2007, p. 679). “Diagnosis of Gaucher disease is based on history, clinical evaluation, laboratory investigations and diagnostic imaging” (Bhengu, 2011, p. 697). According to the South African Guidelines for management of Gaucher disease, it is apparent that some baseline assessments need to be conducted: “history, including family pedigree, medical history of bone involvement” (Bhengu, 2011, p. 697), infections, history of bruising, blood transfusions and nose bleeds (Bhengu, 2011, p. 697).

Diagnostic methods often also involve ultrasound for organ measurement and “cardiac ultrasound for the detection of pulmonary arterial hypertension” (Wang, 2011, p. 464). “Magnetic resonance imaging (MRI) is utilised for the initial evaluation and subsequent monitoring of hepatosplenomegaly” (Wang, 2011, p. 464). Other diagnostic measures include “radiography and bone scintigraphy to detect bone lesions and complications” (Wang, 2011, p. 464), as well as “osteodensitometry for evaluation of osteopenia of the lumbar spine and femoral neck” (Wang, 2011, p. 464). An increase in certain “biological markers” (Wang, 2011, p. 464), that are important both for the initial diagnosis and monitoring with or without treatment, is also observed such as “chitotriosidase, angiotensin converting enzyme, ferritin and tartrate-resistant acid phosphatases” (Wang, 2011, p. 464). Diagnosis can be confirmed by demonstrating a deficit in the “enzymatic activity of glucocerebrosidase” (Wang, 2011, p. 464). “In rare cases, genotyping may be of prognostic value: a patient with a homozygous N370S mutation in the *GBA* gene will not develop neurological disease” (Belmatoug, 2012). “Differential diagnoses include other lysosomal storage disorders. The presence of Gaucher-like cells can be found in certain hematologic diseases (lymphoma, Hodgkin's lymphoma and chronic lymphocytic leukemia)” (Wang, 2011, p. 465) (Belmatoug, 2012).

Gaucher disease can be diagnosed at any age. “The first ICGG Gaucher Registry publication involved 1 698 patients” (Charrow, 2000, p. 2835), ranging “from infancy to older than 90 years” (Mistry, 2015, p. S7). This emphasises the *paediatric* component of type 1 Gaucher disease, since almost “half of the 94% of patients” (Charrow, 2000, p. 2837) participating “in the disease registry were diagnosed before the age of 10” (Charrow, 2000, p. 2835). Lack of “diagnosis and treatment of Gaucher type 1 disease” (Weinreb N. , 2008, p. 890) may result in visceral, haematological and skeletal damage that decrease life expectancy (Weinreb N. , 2008, p. 890). Progression tends to be more abrupt “in patients with early onset type 1 Gaucher disease” (Bhengu, 2011, p. 697) (Martins, 2009, p. S10).

Undiagnosed does not mean un-suffered, and therefore early diagnosis is essential to minimise organ damage through early treatment initiation with a subsequent reduction in mortality, morbidity and enhanced quality of life (physiologically and psychologically). A “diagnostic algorithm for adults has been proposed” (Di Rocco, 2014, p. 1905) by Di Rocco et al to guide haematologists in “providing timely Gaucher disease diagnosis and treatment” (Di Rocco, 2014, p. 1905).

Among children, enzyme replacement therapy can have a particularly positive impact. Results have shown that anaemia and thrombocytopenia normalises within 6 to 8 years, whilst “liver and spleen sizes decrease dramatically with treatment” (Andersson, 2008, p. 1182). Bone crises tend to disappear with treatment. “Although improvement in bone manifestations is slow, average height normalises after 8 years of treatment compared with aged-matched sibling controls” (Andersson, 2008, p. 1182).

#### **4.5 Criteria for treatment of Gaucher disease**

The South African Guidelines for management of Gaucher disease (Bhengu, 2011, p. 698) state that one of the aims of intervention in Gaucher disease patients is first and foremost to avoid irreversible organ (liver, spleen) damage and complications such as bone, pulmonary and neurological complications.



## 4.6 Treatment options

Since “type 1 Gaucher disease is one of the most prevalent lysosomal storage diseases” (Weinreb N. , 2015, p. 2), it was also “the first to be treated successfully with pharmacological enzyme replacement therapy” (Weinreb N. , 2015, p. 2). As already alluded to, early diagnosis and treatment with ERT leads to reduction in liver and organ size, recovery of haematological parameters, and most importantly, prevention and resolution of bone symptoms (Weinreb N. , 2002, p. 112).

“There are not a wide variety of treatment options available for Gaucher type 1 disease” (Bhengru, 2011). ERT for type 1 Gaucher disease has been available for more than 25 years, “since 1991” (Barton, 1991, p. 1264) (Rohrbach, 2007, p. 2697). It was first introduced as a “human placenta-derived enzyme (alglucerase, Ceredase®, Genzyme, Sanofi, Cambridge, MA, USA)” (Hollak, 2012, p. 529) (Znidar, 2014, p. 2) and since “1994, as imiglucerase (Cerezyme®, Genzyme), a human recombinant form of the enzyme” (Hollak, 2012, p. 529) (Znidar, 2014, p. 2). “A second recombinant human enzyme replacement therapy, velaglucerase-alfa (Vipriv®, Shire Human Genetic Therapies, Dublin, Ireland)” (Hollak, 2012, p. 529) (Znidar, 2014, p. 2) and “a third, taliglucerase alfa (Elelyso™, Protalix Carmel, Israel)” (Znidar, 2014, p. 2) “which is a plant cell-expressed acid  $\beta$ -glucocerebrosidase, was approved in the United States and other countries in 2012” (Rosenbaum, 2014, p. 2). Eligustat tartrate is a novel oral treatment for Gaucher disease recently launched in Europe. “Enzyme replacement therapy: imiglucerase” (Cerezyme), the “analogue of human intracellular glucocerebrosidase”, administered intravenously over a 1 to 2 hour period, “is the treatment of choice for type 1 Gaucher disease” (Bhengru, 2011, p. 698). This is also “the only product currently registered” (Bhengru, 2011, p. 698) and available “in South Africa” (Bhengru, 2011, p. 698) for treatment of Gaucher disease.

Dosages should be individualised to each patient on an individual basis. This “may be increased or decreased depending on various clinical manifestations” (Bhengru, 2011, p. 698) and achievement of therapeutic goals.

According to Mistry et al, patients who received timely treatment with imiglucerase “within 2 years of diagnosis” (Mistry, 2009, p. 561) demonstrated “a significantly decreased incidence” (Mistry, 2009, p. 561) of “avascular necrosis” (Mistry, 2009, p. 561). In addition, not only does imiglucerase significantly improve bone mineral density, it also “decreases the risk of skeletal events” (Sims, 2008, p. 439) such as “fractures, lytic lesions and infarctions” (Sims, 2008, p. 439). Imiglucerase also significantly reduces bone pain within 3 months and bone crises within 12 months (Sims, 2008, p. 430).

According to the “South African guidelines for management of Gaucher disease” (Bhengu, 2011, p. 699), a pregnant patient may be “treated with enzyme replacement therapy” (Bhengu, 2011, p. 699) for the full gestational period (Bhengu, 2011, p. 699). If patients decline the pharmacological treatment option of enzyme replacement therapy, other supportive therapy including analgesia, bisphosphonate therapy and supportive intervention with blood products may be considered. Mobility aids like crutches and wheelchairs can also be used.

Patients should ideally be monitored every 6 months for disease progression.

#### **4.7 Mortality**

Mostly, “the clinical course and life expectancy” (Pastores, 2004, p. 4) of type 1 Gaucher disease “are extremely variable” (Pastores, 2004, p. 4), “encompassing a spectrum ranging from wide-ranging disease presenting early in childhood” (Pastores, 2004, p. 4) to an indolent or sometimes “asymptomatic disorder discovered unexpectedly in elderly adults” (Pastores, 2004, p. 4). Mostly, the disease is progressive, although at dissimilar rates. “Symptomatic patients may die prematurely due to consequences of severe crippling skeletal disease, bleeding complications, infection or liver failure” (Pastores, 2004, p. 5).

Sometimes disease progression can be quick and relentless, whilst at other times, gradual and “erratic, punctuated by periods of rapid exacerbation and clinical crises interspersed with sometimes long periods (sometimes lasting for months or even many years) of dormancy” (Pastores, 2004, p. 5).

“Disease severity may even be individually unevenly distributed according to different organ compartments” (Pastores, 2004, p. 5), attacking different organs at different times with major disparities in disease severity (Pastores, 2004, pp. 4,5). Weinreb et al found that “estimated life expectancy at birth for Gaucher disease type 1 patients was approximately 9 years less than for a reference population” (Weinreb N. , 2008, p. 896), based on US (developed nation) data (Weinreb N. , 2008, p. 896).

Some authors even suggest an intrinsic association of type 1 Gaucher disease with multiple cancers (Lo, 2010, p. 340) (Taddei, 2009, p. 208), cerebrovascular as well as cardiovascular events, and hence contributing to a decreased life expectancy in these patients (Zimran, 2011, p. 1468). Insulin resistance, splenectomy, altered iron metabolism and immune dysregulation, are some of the factors thought to contribute to the development of malignancy (Nagral, 2014, p. 41).

## **4.8 Morbidity**

### **4.8.1 Physical consequences of Gaucher disease**

Due to the progressive “course of type 1 Gaucher disease” (Hughes D. , 2007, p. 676) it “may result in pathological characteristics that may become problematic” (Genzyme Gauchercare, 2016) or even irreversible. “Manifestations may be severely debilitating and disabling or even fatal as a result of haemorrhage, sepsis, and other infections, malignant neoplasms and progressive liver and pulmonary disease” (Genzyme Gauchercare, 2016).

According to Charrow et al, long-term consequences may include (Charrow, 1998, p. 1754):

- Hypersplenism (overactive spleen), spleen infarcts (occlusion of the splenic vascular supply), spleen scarring, and formation of nodules (abnormal swelling or aggregation of cells)

- Advanced liver disease with fibrosis (pseudo cirrhosis) (liver damage and scarring), “portal hypertension” (Bandyopadhyay, 2011, p. 801) (an increase in the blood pressure within a system of veins called the portal venous system), “oesophageal varices” (Henderson, 1991, p. 346) (abnormal, enlarged veins in the lower part of the oesophagus), and hepatocellular cancer (liver cancer)
- Advanced bone involvement with progressive deterioration and eventual irreversible disability
- “Pulmonary hypertension” (Bouquila, 2012, p. 58) (elevated blood pressure in lung arteries) (Charrow, 1998, p. 1754).

Consequently, Mistry et al caution that “prompt diagnosis, before the occurrence of irreversible complications,” (Mistry, 2011, p. 110) is critical in the successful management of Gaucher disease (Mistry, 2011, p. 110). According to Di Rocco et al “irreversible complications occur in approximately 25%” (Di Rocco, 2014, p. 1905) of Gaucher disease “patients who do not receive timely therapy because of late diagnosis” (Di Rocco, 2014, p. 1905).

However, many patients’ clinical history reveals previous misdiagnoses that include leukaemia (cancer of the body’s blood-forming tissues, including bone marrow and the lymphatic system), immune thrombocytopenic purpura (a bleeding disorder affecting blood platelets), autoimmune disease (when the body’s immune system destroys healthy body tissue), hepatic cirrhosis (long-term liver damage), idiopathic avascular necrosis (cellular death of bone components resulting from interruption of blood supply due to an unknown cause), viral disease, idiopathic splenomegaly (overactive spleen due to an unknown cause) and anaemia of chronic disease (lower than normal red blood cells due to a chronic infection, immune activation or malignancy). Misdiagnosis leads to complications such as avascular necrosis, osteopenia, liver disease, and bleeding complications as well as inappropriate procedures such as splenectomy, liver biopsy and empirical corticosteroid therapy (Mistry, 2011, p. 110).

Mistry et al noted that for many patients subsequently diagnosed with Gaucher disease, there seems to be a huge time gap between symptoms and diagnosis (Mistry, 2007, p. 679). Because of the rareness of type 1 Gaucher disease many physicians also seem to lack familiarity with recognition, diagnosis and treatment (Weinreb N. , 2013, pp. 24-43). Gaucher patients are therefore more susceptible “to lack of access to timely and appropriate medical care” (Mistry, 2007, p. 697). In order to establish timing of diagnostic delays, Mistry et al conducted surveys in 136 type 1 Gaucher disease patients. In this patient group, results indicated that the “average time from first manifestation of symptoms to final diagnosis was  $48,7 \pm 123,6$  months” (Mistry, 2007, p. 697). Mistry et al reported that “14 patients with type 1 Gaucher disease” (Mistry, 2007, p. 697) endured “symptoms for up to 10 years before correct diagnosis” (Mistry, 2007, p. 697) was made in order to elucidate actual consequences of diagnostic delays, a finding substantiated by Di Rocco et al (Mistry, 2007, p. 699). Di Rocco et al found that Gaucher disease often continues to be unrecognised for many years transpiring in significant delays in advantages of treatment with subsequent development of irreversible complications. This transpires even though the greater part of “signs and symptoms of Gaucher disease” (Di Rocco, 2014, p. 1905) mostly appear in early childhood of most patients (Di Rocco, 2014, p. 1905).

Gaucher disease is often characterised by a lack of strength (asthenia), delayed growth “(growth retardation) or delayed puberty” (Bhengu, 2011, p. 699). Most patients may also develop an enlarged spleen (splenomegaly) “that may be complicated” (Charrow, 2000, p. 2835) by interruption of the splenic blood supply (sometimes superinfected). “In the ICGG Registry 87% of Gaucher patients had splenomegaly in excess of 5 times normal” (Charrow, 2000, p. 2835). An enlarged liver (hepatomegaly) is “frequently” (Lachmann, 2000, p. 239) encountered in Gaucher patients. Belmatoug reported a prevalence of “80%”. (Belmatoug, 2012) This may progress towards fibrosis (scarring) followed by cirrhosis (long-term damage) in rare cases (Bhengu, 2011, p. 699).

Blood disorders like “pancytopenia” (Belmatoug, 2012) (reduction in red blood cells, white blood cells and blood platelets) occurs frequently and is associated with various degrees (sometimes severe) of thrombocytopenia (low blood platelet count) and anaemia (Belmatoug, 2012).

Gaucher disease also increases “risk of developing Parkinson’s disease later on in life” (Henneman, 2016) (Becker, 2013, p. 129) (Platt, 2014, p. 68). According to Rosenbloom et al, “the probability that a patient with type 1 Gaucher disease will develop Parkinsonism before age 70 years is 5 to 7% and 9 to 12% before age 80 years” (Rosenbloom, 2011, p. 95). Although the pathophysiology that results in type 1 Gaucher disease “patients developing Parkinsonism is still not well understood” (Rosenbloom, 2011, p. 101), and many patients “are not likely to manifest Parkinsonism during their expected lifetime, the incidence of Parkinsonism among GD1 patients is nonetheless significantly increased” (Rosenbloom, 2011, p. 101).

#### **4.8.2 Bone implications**

“Skeletal disease is complex and multifaceted, manifesting as chronic bone pain, severe, acute avascular osteonecrosis, medullary infarction, osteopenia, osteoporosis, osteolytic lesions, pathologic fractures, and growth failure in children” (Mistry, 2015, p. S8).

“Overall skeletal involvement makes the largest contribution to morbidity, disability” (Mistry, 2015, p. S6) and quality of life in type 1 Gaucher disease patients (Mistry, 2015, p. S6). Mistry et al reported that osteopenia can develop as early as 5 years of age (Mistry, 2011, p. 139). Children with Gaucher disease may also suffer from growth deficits and pubertal delays as well as considerable bone pain and bone crises. In many instances bone pain is diagnosed too late and, as previously alluded to, could lead to life-threatening fractures, or even avascular necrosis of the hips. Avascular necrosis “can lead to joint destruction, the need for joint replacement surgery, and chronic disability, increasing the already huge social and financial burden” (Mistry, 2009, p. 561).

The majority (80%) of patients with Gaucher disease present with bone anomalies. Some of the signs are “deformations, osteopenia that sometimes causes pathological fractures or vertebral compression, bone infarctions or even aseptic osteonecrosis” (Belmatoug, 2012).

“Patients may experience severe bone pain, called “bone crisis,” because Gaucher cells in the bone marrow may prevent blood from circulating properly” (Belmatoug, 2012). Pain can be excruciating, and is frequently accompanied by fever that may last up to a few weeks. Patients are often debilitated and remain bedridden during this time. As Gaucher cells accumulate in bone marrow, they can restrict normal blood flow—sometimes to the point that bone tissue dies. This bone destruction causes severe pain and can lead to fractures and joint collapse. “Type 1 Gaucher disease can also cause reduced mass and density of bone tissue, resulting in thin and weakened bone that is more susceptible to fractures. Gaucher disease causes abnormalities in the way bones develop, causing them to form irregular shapes” (Belmatoug, 2012). “The Erlenmeyer flask deformity (so named because its shape resembles a type of laboratory flask), in which the ends of the bone (most commonly the femur and tibia leg bones) are flared and flattened rather than rounded” (Belmatoug, 2012) is very commonly encountered. Morbidity due to bone manifestations can cause extremely reduced quality of life due to the risk of “bone crises” and bone fractures. Quality of life is also influenced by the cost of hospitalisation, days lost to unproductivity and loss of earning potential, as well as the risk of severe hospital-acquired infections, which could obviously decrease a patient’s life expectancy (Belmatoug, 2012).

Physical health is clearly beneficial to its possessor, and preferable to illness. Simultaneously, the proper functioning of physical organs is imperative to the needs of any human being, and obviously intrinsically pleasurable (Norman, 1998, p. 15). The question begs thus, what general formula can we find that will satisfy all three of these conditions? *Living your life efficiently* might well thus define a life of excellence in accordance to being a *complete life*. Thus, a patient with Gaucher disease who is timely diagnosed and receives adequate enzyme replacement therapy might be a good candidate for increased quality of life and also a more complete and fulfilled life, reaching their full potential as an individual, and making a meaningful contribution to society (Masek, 1999).

#### **4.8.3 Psychological, social and quality-of-life consequences**

Symptomatic “Gaucher disease may diminish patients’ emotional feelings of well-being” (Genzyme Gauchercare, 2016) (Damiano, 1998, p. 373) and functional health (GaucherAssociationUK, 2016) (Genzyme Gauchercare, 2016) (Meikle, 1999, p. 281).

According to Gaucher disease patients, the most debilitating physical symptoms interfering with schoolwork, social and work life are chronic fatigue and bone pain (Hayes, 1998, p. 531) (Charrow, 2004, p. 112).

Giraldo et al reported interesting observations regarding self-perception in patients with Gaucher disease (Giraldo, 2005, p. 453). The authors recorded their observations after applying the SF-36 health survey questionnaire twice; prior to starting “enzyme replacement therapy and after 2 years of enzyme replacement therapy in 69 type 1 Gaucher disease patients” (Giraldo, 2005, p. 453). At baseline the patients showed severe restriction in physical functioning scores. Additionally, “improvement in self-perception of global health was observed, from 34.3% before enzyme replacement therapy to 91.4% after enzyme replacement therapy ( $p < 0.001$ )” (Giraldo, 2005, p. 453). The authors concluded that benefits derived from enzyme replacement therapy “are cumulative and accrue over the course of the follow-up of disease assessed over 2 years” (Giraldo, 2005, p. 461).

Similar reports from other studies suggest “that early intervention, prior to advanced Gaucher disease offers the best possibility of good outcome” (Giraldo, 2005, p. 461) (Masek, 1999, p. 263).

“Emotional issues relating to Gaucher disease can put strain on individual patients and their entire families” (Genzyme Gauchercare, 2016) (Hayes, 1998, pp. 526,527). Hayes et al reported on “patients' health-related quality of life (HRQoL) of patients with Gaucher disease” (Hayes, 1998, p. 521). The authors “interviewed 16 patients with type I Gaucher disease (range 8-67 years)” (Hayes, 1998, p. 522). Thirteen out of 16 patients “had been receiving enzyme replacement therapy for at least 6 months” (Hayes, 1998, p. 521). The following factors related to quality of life were studied: “physical health, social life, emotional health, financial burden, future plans and satisfaction with health care” (Hayes, 1998, p. 521). Hayes et al reported that when the 16 Gaucher disease patients who received enzyme replacement therapy but without splenectomy were asked how Gaucher disease affected their physical activity, eight (50%) indicated that the disease had a definite effect on their job/schoolwork or household/family obligations. Two (29%) of the patients who received enzyme replacement therapy and had a splenectomy, reported an effect on their schoolwork or jobs, whilst 4 (67%) reported an impact on their job and family obligations (Hayes, 1998, pp. 526,527).



These results indicated that Gaucher patients included in this study were most incapacitated by “bone pain and chronic fatigue” (Hayes, 1998, p. 521) which “interfered with school, job and social activities” (Hayes, 1998, p. 521). Thus, Gaucher disease can ultimately also impact quite severely on quality-of-life (Hayes, 1998, p. 521). Patients reported “a significant increase in energy level” (Hayes, 1998, p. 521) from enzyme replacement therapy as well as “significant improvements in quality of life” (Hayes, 1998, p. 521). Although therapy had a significantly “positive influence on the patients’ health-related quality of life” (Hayes, 1998, p. 521), anxiety related to the means of financing treatment, added additional emotional distress to these patients (Hayes, 1998, p. 532).

A common occurrence in children with type 1 Gaucher disease, is growth restriction and “delayed onset of puberty” (Charrow, 2004, p. 112). Half “(50%) of the symptomatic children are at or below the third percentile of height” (Charrow, 2004, p. 112) and 1 in 4 “(25%) are shorter than expected” (Charrow, 2004, p. 112).

Patients may be confronted with feelings of inferiority because smaller stature and “body image can be a difficult challenge” (Grabowski, 2004, p. 61) for individuals “who have an enlarged spleen and/or liver” (Grabowski, 2004, p. 61). Children during formative years, especially “children who may already suffer from a negative self-image” (Genzyme Gauchercare, 2016) or low self-esteem may find this exceptionally difficult.

Emotional issues associated with Gaucher disease can become increasingly disconcerting for children who are at an age where it is imperative for the child to “fit in” with their peers. (GaucherAssociationUK, 2016). Paediatric patients may also “experience feelings of anger, denial, fear, insecurity and isolation” (Grabowski, 2004, p. 61). Thus, delay in growth and puberty at the adolescent age in comparison with their peers, can be a source of significant anxiety and stress to patients and their families (Kauli, 2000, p. 162). As previously mentioned, it is important to note that, amongst others, Andersson et al reported that growth in children responds well to enzyme replacement therapy (Andersson, 2008, p. 1182). Counselling and encouragement for healthy socialisation skills might be necessary in these children.

Chronic pain and “fatigue may affect school performance and participation in physical activities” (Charrow, 2004, p. 112). Results from a study by Hayes et al indicated that 88% of patients included in a HRQoL study reported being easily fatigued (Hayes, 1998, p. 525). As a consequence of the fatigue associated with anaemia, “some children may even lack the energy and stamina to play with other children” (Genzyme Gauchercare, 2016) and even find it difficult to fulfil ordinary tasks like concentrating on homework (Genzyme Gauchercare, 2016). Depending on the severity of the disease, children and adults with Gaucher disease might have ever increasing physical and emotional needs.

Masek et al investigated the long-term (2-year) “effect of enzyme replacement therapy on health-related quality of life in 25 adults with type 1 Gaucher disease” (Masek, 1999, p. 263). Quality of life assessment was conducted with the “SF-36 Health Survey (SF-36)” (Masek, 1999, p. 263) whilst “psychological functioning was assessed using the Symptom Checklist 90R” (Masek, 1999, p. 263).

Results indicated a statistically “significant improvement in most (7 of 8) SF scale scores starting at 18 months of therapy” (Masek, 1999, p. 263). Vitality (energy level and fatigue) accounted for the first SF scale showing statistically significant improvement at 6 months of therapy. Role-Physical and Social Functioning indicated the SF-36 scales with the largest improvements. Masek et al also reported a “significant improvement in mood and global functioning and fewer psychological symptoms” (Masek, 1999, p. 263) after 2 years of therapy. Ultimately, the authors conclude that “enzyme replacement therapy for type 1 Gaucher disease has a positive impact on health-related quality of life from the patient's perspective” (Masek, 1999, p. 265).

Damiano et al interviewed 212 patients, 14 years and older treated with “enzyme replacement therapy from 1 to 51 months” (Damiano, 1998, p. 373). The authors utilised the SF-36 health survey and three questions about physical, mental and general “health related quality of life (HRQoL)” (Damiano, 1998, p. 373) since starting enzyme replacement therapy were asked. When asked about “changes in health related quality of life (HRQoL)” (Damiano, 1998, p. 373) since starting enzyme replacement therapy, at least half of the patients reported fewer limitations in physical activities (53%), better general health perceptions (77%) and less negative emotions (49%) at the time of the interview (Damiano, 1998, p. 373).

A study by Packman et al revealed a number of “psychosocial needs and concerns” (Packman, 2010, p. 2002) commonly experienced by Gaucher disease patients (Packman, 2010, p. 2002). These include: difficulty to cope with diagnosis, detrimental effects of fatigue and pain on the jobs, careers and recreational activities of patients, financial concerns due to lack of insurance concerns as well as psychological distress (Packman, 2010, p. 2008). McAllister et al proposes “ecology of social impact variables, including associated burdens, sequelae and emotional manifestations in rare genetic conditions” (McAllister, 2007) (Wienke, 2014, p. 80). According to Packman, the genetic condition and subsequent burden of disease include, amongst others, the lack of access to and sharing of information, lack of public knowledge and genetic fatalism and/or determinism. These may lead to important primary sequelae. Diagnostic delay, explanation fatigue, fears for future generations, impact on job status and health and payment systems, are only some of the many primary sequelae associated with rare diseases. These may further manifest in vindication, provider mistrust, fear for self and children, as well as guilt and misconceptions and uncertainty.

Although the full social impact of dealing with Gaucher disease has not been clearly described as yet, Wienke et al “developed a model to explain the social impacts of another rare genetic disorder, alpha-1 antitrypsin deficiency (AATD)” (Wienke, 2014, p. 75). According to the author, this model may assist in “future development of psychometric instrumentation to measure the social burden of similar rare diseases with a genetic etiology” (Wienke, 2014, p. 75). Two pilot studies were conducted and “interviews with 42 patients and caregivers living with AATD were collected” (Wienke, 2014, p. 75). The results of the study by Wienke et al, suggests refinements and expansion to the conceptual framework proposed by McAllister et al (Wienke, 2014, p. 80). An example of Wienke’s thematic synthesis is that the impact domain such as genetic etiology can potentially lead to genetic determinism (where genes, along with environmental conditions determine morphology and behavior) and/or genetic fatalism (genetic basis of a trait perceived to be unchangeable). This may in turn impact all relationships. The participant experiences a lack of control and perceives the gene to determine their future. Possible psychological sequelae of this include fear not only for future health but also fear for many generations to come and hence adaptive behavioral modifications towards extreme vigilance.

Similarly, not only does sharing of genetic information consign the responsibility to inform family members about risks, it can also adversely affect patient/family relationships and lead to “testing decisions, guilt, and fear for future generations and strain within the family dynamic” (Wienke, 2014, p. 78).

Future research specifically focusing on Gaucher disease, might also shed additional light on the social impact of this rare and chronic genetic condition on patients.

As with any other rare disease, genetic counselling of the family (parents, siblings and affected individuals) is of the utmost importance. It supplies supportive care for the family and is best provided by a physician that has experience with Gaucher type 1 disease. Counselling also enables the family to understand the role of inheritance, strategies to prevent recurrence and best possible scenarios, providing couples with knowledge and control in order to make informed decisions (Bhengu, 2011, p. 698) (Zuckerman, 2007, p. 1281).

It is a well-known fact that the shortage of trained genetic professionals (geneticists and genetic counsellors) leaves much of the population without access to appropriate services (Beighton, 2012, p. 447). In addition, because rare diseases occur with smaller prevalence, national health programs do not seem to prioritize funding for these diseases. Without clear, transparent treatment guidelines and predictable reimbursement policies, some patients with rare diseases may unfortunately face an uncertain future.

## Chapter 2

### **Type 1 Gaucher disease and associated ethical issues**

#### **1. Resource Allocation**

##### **1.1 Introduction**

One of the most unequivocal and compelling implications of equal opportunity, lies in the realm of fair and just healthcare. The fundamental principle is that a fair and just healthcare system should strive to eliminate obstacles to opportunity as a result of disease, i.e. utilising an intervention to timely recognise, diagnose, cure or prevent the disease (Buchanan, 2000, p. 16).

It is virtually and certainly materially unviable to provide the best possible healthcare for every single patient, especially in resource constrained settings (Mosadeghrad, 2014, pp. 83, 84). If this endeavour takes place whilst both trying to provide individuals with a freedom of choice *and* guaranteeing equal care, the dream of containing costs of health care is a most definite impossibility. Engelhardt is of the notion that the difficulties in achieving a nirvana of equality can mainly be attributed to the competing views regarding beneficence, inequalities and justice. It requires a careful balancing act between those who have and those who need. Engelhardt compares this to "a coercive act of totalitarian ideological zeal" which does not take into account any diversity or multiplicity of moral vision (Engelhardt, 2014, p. 645). Engelhardt deems that the road in pursuit of equality has numerous practical and moral obstacles and no one should be held accountable or feel morally and socially obliged to aid those individuals, who suffer due to drawing the shortest stick in the natural lottery of life.

Treatment of rare diseases like Gaucher disease are invariably highly priced; healthcare policymakers are continuously presented with unrelenting challenges regarding resource allocation for these orphan drugs (McCabe, 2005, p. 1016) (Hughes D. , 2005, p. 315).

We should be mindful of the fact that limiting the access of orphan medicines to patients who suffer from a rare disease will result in this group of patients, being left untreated. Conversely, in choosing to reimburse an expensive orphan drug, this may result in a considerable number of patients with a more prevalent disease being deprived of more cost-effective treatments. This contradiction in terms raises important questions on social justice and fairness (Hughes D. , 2005, p. 315). Equality surely necessitates “that we do not discriminate between individuals on morally irrelevant grounds” (McKie, 2003, p. 2407). Cost should therefore not be considered the only determining factor for access to medicine.

The complexity of decision-making seen in resource allocation, when we treat patients with a rare disease such as Gaucher disease as an excellent example, reflects many of the multifaceted issues of dealing with expensive and limited health-associated resources (Brock, 2006) (Panju, 2010, p. 182) (Gross, 2002, p. 151) (Bastias, 2011). Because of their wide-ranging physiological as well as psychological ramifications, rare diseases “require an ongoing multi-disciplinary team approach to treatment” (Wang, 2011, p. 458) which increases costs considerably (Wang, 2011, p. 458). Some health systems even “demand that each new therapy be demonstrated to be cost-effective” (Wang, 2011, p. 459) which may prove an arduous task for rare diseases (Wang, 2011, p. 459).

Starting with the burden and cost of treating a rare disease like Gaucher disease, the following discussion of ethical principles pertinent to resource allocation in healthcare will highlight why a one-dimensional approach is insufficient in patients diagnosed with Gaucher disease.

## 1.2 The burden and cost of treating Gaucher disease

High cost treatments are usually challenged because they seem less cost-effective versus treatments perceived to be costing somewhat less. When looking at placing a value on health, there are two schools of thought. Daniels et al hold that health deserves priority funding in relation to other public goods (Daniels, 2008).

However, other authors are of the opinion that health as well as other public goods that impact on health, are closely connected and therefore priority should not only be given to healthcare alone (Segall, 2010) (Wilson, 2009).

Mavroudis et al hold that “most models are designed to inform policy decisions by quantifying aspects of resource allocation” (Mavroudis, 2015, p. 1623) which are seemingly immeasurable, like “benefits to society of treating certain” (Mavroudis, 2015, p. 1623) disorders, “the value of an individual life” (Mavroudis, 2015, p. 1623), as well as “the difference in a human life’s worth” (Mavroudis, 2015, p. 1623) when taking into consideration significant morbidity. It is, however, infinitely easier to quantify treatment costs rather than more abstract concepts such as quality of life (Mavroudis, 2015, p. 1623). It is evident that healthcare resource allocation in a society with limited resources like South Africa, while “ethically troubling” (Mavroudis, 2015, p. 1624), necessitates an explicit estimation or quantification of “human life” (Mavroudis, 2015, p. 1624).

In South Africa, a utilitarian approach is followed by the National Health Department (Hattingh, 2015, p. 17). The utilitarian approach “is important in evaluating different treatment modalities for” (Mavroudis, 2015, p. 1624) more commonly encountered diseases like HIV or tuberculosis; however its use might be much more challenging and even sub-optimal when dealing with rare and costly disorders like Gaucher disease (Mavroudis, 2015, p. 1624). Justifiably, since HIV and tuberculosis are contagious diseases with the potential to infect a large number of people, versus rare diseases from a genetic origin, the total impact on public health could be considerably larger. This has to be taken into consideration when reflecting on the differences in resource allocation for different diseases.

Given the small number of patients diagnosed with Gaucher disease, the total cost impact may be limited. There has been substantial evidence proving that, due to low cost, that it might in actual fact warrant funding (Hughes D. , 2005, p. 832).

Individuals with serious genetic defects may place an additional burden on society. Difficulties face many people with Gaucher disease regarding access to proper treatment, sufficient dosing, and, maintenance of insurance coverage (Wang, 2011, p. 459). The costly treatment raises legitimate questions involving public and private economic considerations for policy makers and healthcare providers, especially regarding access to proper medical care, social justice and suitable allocation of resources (Mayberry, 2006, p. 103).

In this case study, the decision rests heavily on the fact that the newly diagnosed mother (Mrs. X) needs to be on lifelong treatment herself. Using enzyme replacement therapy is expensive, which restricts access to these procedures. Parents with high socioeconomic status or adequate reimbursement from a medical aid may have easier access to this technology. The goal of social justice is to treat each individual with the dignity and respect he/she inherently deserves as a human being and therefore, to try to accommodate these individuals in terms of treatment (WHO, 2002) (Robinson, 2016). However, rare orphan diseases are by definition low prevalence which renders the overall outlay not too excessive when compared with other treatment modalities. According to Esfandiary et al, creating a genetic medicine for serious human diseases does not sacrifice human dignity but rather respects it by “allowing individuals to achieve their potential with an equal opportunity” (Esfandiary, 1998, p. 512).

There are currently 85 patients diagnosed with Gaucher disease in South Africa of which 69 are receiving enzyme replacement treatment (Genzyme, 2016). Note that treatment includes commercial and free treatment (humanitarian assistance, patients who were part of global clinical trials and receive free supply of drug). Ten patients are currently receiving free ERT treatment. The yearly cost of enzyme replacement treatment for the 10 public sector patients with Gaucher disease, who are diagnosed but not treated, is approximately R 7,8 million (Genzyme, 2016). This is not a huge amount if one compares the yearly costs associated with Gaucher disease to that of treatment of, for instance, HIV and TB.



An argument can be made supporting a much stronger role for the public sector in priority setting and allocation of more funding for rare diseases.

With a greater shift to prioritising HIV and TB, budget cuts for amongst others, genetic testing services (which is an essential tool in the diagnosis of congenital disorders) resulting in inadequate staff and equipment have resulted in these services being severely compromised in recent years (Malherbe, 2015, p. 186).

According to UNAIDS (2015), there are currently about 7 million people living with HIV in South Africa (Morah, 2016). Morah further reports that the prevalence rate is 19.2% in adults 15 to 49 years of age. If one considers the high infection rate and the size of its population (more than 54.96 million ([www.statssa.gov.za](http://www.statssa.gov.za)), this proportion is quite significant. HIV/AIDS also has a considerable influence on the economy as well as business and thus receives remarkable attention from both “South African government as well as from the business community” (Ostheimer, 2004).

According to Smart, et al, (2015) the “National Strategic Plan for HIV/AIDS, STIs and TB has a set target that 80% of people living with HIV must be on antiretrovirals (ARVs) by 2016” (Smart, 2015), which is about “4,8 million people” (Smart, 2015). The South African Minister of Health reported that >3 million people are currently receiving treatment for HIV (UNAID Gaps Report 2016). Because so many people are dependent on this medicine, an important consideration is thus cost. Smart et al further reports that currently, “the overall tender covering the three-year period from 1 April 2015 to 31 March 2018 is over R 14,2 billion” (Smart, 2015). This comprises largely of a first-line fixed-dose combination (FDC) of efavirenz/ tenofovir/ emtricitabine. By perusing the Department of Health’s (DOH) purchasing catalogue – which basically gives all the products and their volumes and values on tender - and if one looks at the contribution of HIV treatment to overall value and volume in the tender, just the combination HIV products make up 35% of the total predicted value of the tender (Fuzila, 2015) (Department of Health Purchasing order, 2015).

Similarly, according to Pooran et al (2013), if the National drug resistant tuberculosis guidelines in South Africa are followed, the cost per patient of extensively-drug resistant tuberculosis is approximately R 352 070.00, four times greater than multi drug resistant tuberculosis (R 90 339.00) and 103 times greater than drug-sensitive tuberculosis (R 3 429.00) (Pooran, 2013). Pooran et al further state that “despite drug-resistant tuberculosis comprising only 2.2% of the case burden, it consumed a huge ~32% of the total estimated national tuberculosis budget of R 2.9 billion” (Pooran, 2013). Anti-tuberculosis medicine and hospitalization contribute to “45% and 25% of the DR-TB costs, respectively” (Pooran, 2013, p. 1). Newer data estimates extensively-drug resistant tuberculosis at >1 500 cases per year which is more than double the 741 cases that Pooran et al (2013) included in their calculations (Pooran, 2013).

All resources are scarce and understandably careful consideration should take place to weigh health benefits versus societies’ aspirations. Governments should therefore recognise the inequalities and “vulnerabilities in health status” associated with rare diseases (ICORD, 2012) and should thus endeavour to develop specific policies to address them. All aspects related to rare diseases should be addressed, “including research, clinical care, information resources and development of treatment” (ICORD, 2012). In addition, should health economics be used (if applicable) in affected individuals like the case study of Mrs. X, the holistic spectrum of personal, social as well as economic benefits of treating a rare disease like type 1 Gaucher disease should be strongly considered.

Both the “United Nations Universal Declaration of Human Rights (Article 25.1)” (Forman, 2012, p. 806) and the “International Covenant on Economic, Social and Cultural Rights (Article 12.1)” (Forman, 2012, p. 806) underscore “the right of everyone to the highest attainable standard of physical and mental health” (ICORD, 2012). South Africa functions within a rights-based constitution (e.g. progressive realisation) and changes are anticipated towards universal health coverage whilst still being cognizant of the economic environment as well as societal priorities. Within the South African context, a national healthcare package like the proposed NHI needs to contain essential elements pertinent to the welfare of children’s health and thus include rare diseases. Great strides are also currently being made on compiling an Essential Package of “Health Care for Children in South Africa” (Henley, 2000, p. 601) (EPaCC) (Westwood, 2016).

Bayefsky is of the notion that one of the universal rights of mankind is “health care and treatment” of a “rare” disease (Bayefsky, 1990). In this regard, ICORD stipulates that the following aspects necessitate careful consideration: “non-discrimination”, fairness and equity of access to healthcare (ICORD, 2012). Thus, not focusing only on diseases with high prevalence in South Africa e.g. HIV and tuberculosis, but urgent attention is similarly required to develop novel policies for a lower prevalence rare disease like Gaucher disease, that requires high cost treatment.

On each society rests the onerous decision of allocating resources to different healthcare needs. Even where most people have access to some kind of healthcare, within countries, inequalities in health status continue to persist alongside social and economic inequalities. Decisions of where to allocate health care funds usually rests on cost-benefit and cost-effectiveness analyses (Nussbaum, 1993) (Kuhse, 2009, p. 351). However, these are also open to interpretation since judgement concerns numerous ethical challenges, begging independent consideration of many moral principles rather than a blanket approach of one-size-fits-all.

The most often used metrics of medical benefit used is “quality-adjusted-life-year (QALY) and disability-adjusted-life-year (DALY)” (Kuhse, 2009, p. 353) which unfortunately do not always take life “compromised by symptoms and functional limitations” into consideration (Kuhse, 2009, p. 353). An advantage of QALY and other measures of health-related quality of life is equality regarding benefit where one unit counts the same regardless of who gets the benefit (Kuhse, 2009, p. 355). However, maximization of the sum total of benefits does not necessarily treat people on equal terms, sometimes giving an unfair advantage to patients whose treatment costs are less versus medicines whose costs are more expensive. Treatment access of orphan drugs may produce numerous arduous “conflicts between the claims of individuals to the right of access to treatment versus society at large” (Picavet, 2013). “The principles of equity and non-abandonment imply that” (Picavet, 2013) patients suffering from life-threatening diseases should have access to these medicines, whilst conversely “society may wish to allocate the health budget to interventions with a view to maximizing the health of the population as a whole” (Picavet, 2013). Maximization thus favours larger patient groups treated with cheaper medicines and disfavors small patient groups with rare diseases treated with more expensive treatment modalities.

In this context, Pinxten et al recommend an ethical healthcare framework encompassing a sustainable model with a fair or equitable share for all. The aptly called “Anne of Green Gables” principle based on the philosophy of, amongst others, broad inclusiveness describes possible randomized access for all, including patients with rare diseases including patients suffering from Gaucher disease. Alternatively, Pinxten proposes access for some patients, allocated according to rational priorities as well as budgetary insulation of a guaranteed, though limited share of resources specifically dedicated to rare diseases (Pinxten, 2012). With regards to Gaucher disease, this will allow a fair share of resources to these patients, by bestowing a specific part of the yearly National Health Budget in South Africa to treatment of Gaucher disease patients, with possible annual increases.

If one looks at the utilitarian approach to distributive justice, this equates to ‘bringing the greatest good to the greatest number’ and generally underscores economic evaluations. “When resources are construed as social goods” (Rachels, 2003) as per the utilitarian principle, resource allocation may proceed on a cumulative “basis by evaluating which distribution might produce the greatest amount of good for the greatest number of people” (Rachels, 2003). When resources are limited as is mostly the case in a developing country like South Africa, resource allocation might however become a problem. *A utilitarian theory of justice* depicts that whatever produces the greatest overall good, will be just. However, in the resource allocation scenario, utilitarianism advocates maximization of “utility or happiness of the many, even if it is at the expense of the few or the *individual*” (Mavroudis, 2015). Consequently, utilitarian principles represent society as a whole and seemingly disregard “the needs of the minority or of groups that may require more resources to achieve the same level of utility as the mass population” (Mavroudis, 2015, p. 1623).

As previously alluded to, “cost-effectiveness is, however, not purely an economic concern, because to improve people’s health and well-being is also a moral concern” (Brock, 2006, p. 259) which should thus guide us towards “the importance of equitable attention and access to treatment for a rare disease” (ICORD, 2012) like Gaucher disease. The ethical dilemma is how to create equilibrium between all the different ethical principles. Often overlooked is the fact that managing any health care resource, at either the individual or population level, involves copious conflicting ethical considerations and moral obligations, especially with regards to distributive justice (Gandjour, 2015, p. e44) (Daniels, 2014, p. 599).

### 1.3 Resource allocation and justice

In this section, the following theories of justice pertinent to resource allocation in rare diseases are discussed. The *principle of distributive justice* becomes crucial where resource allocation with regards to equal distribution of scarce resources, becomes challenging. The *liberation theory of justice* is important due to freedom of choice of goods. Furthermore, resource allocation should ideally be fair, according to the *egalitarian theory of justice* and should benefit everyone equally.

Aristotle was the first philosopher who introduced “the principle of distributive justice, the proper distribution of benefits and burdens” (Beauchamp, 2013). According to Aristotle “equals must be treated equally and unequals must be treated unequally” (Beauchamp, 2001, p. 227).

John Rawls is, however, deemed as one of the most significant and influential political and moral philosophers of the twentieth-century. He is primarily known for his book *A Theory of Justice*, in which he attempts to define social justice through a social contractual approach (Rawls, 2009). Rawls believed that each person has his/her own potential and abilities to fulfil. Rawls proposed “*justice as fairness*” which equates to a basic agreement of what is fair with regards to social cooperation between equal persons. He believed that justice commonly requires that unless a disparate distribution is to everyone’s advantage, basic social goods, for example opportunity and liberty, “income and wealth, and the” basis “of self-respect”, be dispersed evenly between persons (Freeman, 2003, p. 1). Rawls’ work was mostly based on the fundamental principles of what the most appropriate and feasible moral conception of *justice and fairness* would be for a democratic and free society, thereby ensuring *equality* for all citizens (Freeman, 2003, p. 2). Rawls believes “that the basic structure of society is the principal subject of *justice*” (Freeman, 2003, p. 4).

Rawls recognizes two main principles: the first that each person should have equal rights consistent with other people enjoying similar liberties; and secondly, that inequalities should be so arrayed that *no person is unfairly disadvantaged*. He thus developed an egalitarian notion of justice that would allow *fairness* and *equal opportunity* to people born with fewer advantages and into less favourable social positions (Rawls, 2009).

Rawls' principle of distributive justice does not necessarily mean that fairness of distribution is only dependent on merely imposing present status quo thereby giving each person his or her due (Freeman, 2003, p. 6). He believes that "people should be held responsible for their ends" (Freeman, 2003, p. 8) and envisaged that they "adjust their desires to the fair share of resources they can legitimately expect" (Freeman, 2003, p. 8). Rawls deemed his *theory of justice* as an alternative and even superseding that of utilitarianism. Thus, John Rawls deems that every person should be provided an equal opportunity (Buchanan, 2000, p. 16). Rawls believes that any factors which might limit a person's opportunity should be eliminated or ameliorated in order to equalize the playing field. Rawls is of the opinion that justice is not essentially related to restoring disparities inflicted by misfortune or birth, but that justice is predominantly about providing each person with "*adequate means in order to fulfil their 'moral powers' of free, responsible, and rational agency*" (Denier, 2007, p. 153).

The notion of *distributive justice* becomes increasingly critical in situations where there is augmented contest for scarce resources. Equitable and reasonable dispersal of resources is predominantly essential in developing countries like South Africa. According to Beauchamp et al, distributive justice deals with the "fair, equitable and appropriate distribution by justified norms that structure the terms of social cooperation" (Beauchamp, 2013). According to this principle, it would thus obviously be unjust to withhold treatment in a patient just "because their disease is rare" (Picavet, 2012, p. 116) or treatment expensive. Thus, if applying the distributive justice principle in the rare diseases arena, Reidenberg et al held that the definition of "an *essential* medicine" should "be changed to include medicines needed for people with rare diseases" (Reidenberg, 2006, p. 686). Thus, "distributive justice" (Reidenberg, 2006, p. 686) can be used as a moral basis for such a change and cost-effectiveness analysis can be the method used to select which medicines to include in the "Model List" (Reidenberg, 2006, p. 686).

According to Brock et al, resource allocation in health is usually based on two pivotal ethical criteria, namely *cost-effectiveness* and *justice (equitability)*, keeping in mind that resources should also be allotted to maximize health benefits (to improve health) for the population served. Thus, morally, improving people's health and well-being should also be taken into consideration, deviating from the general idea that cost-effectiveness should solely revolve around economic concerns.

In lieu of the ignorance towards improving benefits specifically relating to health and well-being, the philosophical notion of utilitarianism or consequentialism, are widely criticized, by amongst others, John Rawls (Brock, 2006, p. 259). According to Rawls, “the difference principle” (Freeman, 2003, p. 8) dictates what a person may justly and legitimately insist on. This means that everyone should receive enough means in order to fulfil “everyone’s capacities for free and responsible agency” (Freeman, 2003, p. 8).

*Justice* focuses on fairness and equity in the distribution of health resources: a pertinent example for instance, is that those who have little socioeconomic power should receive similar care to those who have more socioeconomic power. “Justice is the assurance that all people receive fair and equal treatment” (Lea, 2005, p. 237) (Beauchamp, 2001, p. 165).

In fact, according to Putoto et al, in recent years the “notion that public opinion can influence the decision making process has gained momentum” (Putoto, 2011).

Being cognizant of public opinion in healthcare matters, which might sometimes differ from the opinions of doctors and policy makers, forces decision makers to take account of objectives according to need, and supports social interconnection and civil identity. This is one of the pivotal rights of an individual belonging to a democratic society. Important to note is that “public debate should be based on” (Putoto, 2011, p. 65) pertinent and precise “information and communication, and be open and transparent with all stakeholders” (Putoto, 2011, p. 65). A *libertarian theory of justice* deals with distribution of property based on individual liberty and freedom of choice, thus entitlement. Nozick maintains that resources should ideally not be allocated by a central distributing authority in a free society (Nozick, 2013, p. 149). According to him, people should be allowed to confer resources to others according to their own desires (Nozick, 2013, p. 223) In this regard Rawls and Nozick have totally different and even conflicting world views of what should be considered as justice or fairness. For Rawls, each person has an equal right based on basic liberties, whilst in contrast, Nozick believes that one simply owns things, and thus has entitlements.

An *egalitarian “theory of justice”* (Rawls, 2009, p. 302) as described by “Rawls (1971)” in “A Theory of Justice” depicts a system of cooperation for equal and fair distribution of goods to everyone’s advantage (Rawls, 2009). Rawls relates his theory to equal rights in terms of liberty as well as equality of opportunity (Rawls, 2009, p. 302).



Norman Daniels created an “*egalitarian theory*” which expanded Rawls’ “theory of justice” into the domain of “health and health care” (Daniels, 2014, p. 599). His egalitarian theory serves as a justification to safeguard parity of opportunity through widening the scope by introducing policies aimed at sustaining people as near as possible to normal human functioning and hence establishing fairness and equality in terms of health (Daniels, 2014, p. 599). Daniels argues that this will safeguard a person’s fair share of available opportunities in society. It is imperative to grant people the opportunity, through normal health and functioning, to contribute fully and hence to take part in all domains of life, including social, economic as well as political societal life (Daniels, 2014, p. 599).

The association between healthcare and the protection of opportunity suggests distributive justice as an appropriate principle of protecting fairness of opportunity. Healthcare is thus of special moral significance since it facilitates our status as fully functioning human beings and therefore deserves a fair process of rationing (Daniels, 2014, p. 609). Daniels holds that aggregate conditions, circumstances and knowledge gathered during a person’s life create health. Thus health is not only created by getting medicine for treatment and prevention (Daniels, 2014, p. 611). Managing or preventing any disease, like Gaucher disease, should involve holistic medicine, which comprises consideration of the entire individual, including physical, psychological, spiritual as well as social circumstances. It also involves well-being, quality-of-life as well as the happiness of the person. All these dimensions are interrelated and equally significant. One should thus reflect not only on the physical state of the patient caused by the disease, but rather regard the patient as a whole, including his or her current state-of-mind, emotional circumstances and social environment, thus recognizing the individual as an aggregate human being.

Justice underscores the essential equivalence of all human beings. Ronald Dworkin (1977: 227) distinguishes between “the right to equal treatment” referring to equivalent dissemination of resource or opportunity versus “the right to treatment as an equal” ergo “the right not to receive the same distribution of benefit, but to be treated with the same respect and concern” as everyone else (Dworkin, 1977, p. 227). Dworkin argues that “the right to treatment as an equal” is much more fundamental. A Gaucher patient has the right to have an equal expectation for treatment in line with the current treatment given to a tuberculosis or HIV patient.



As soon as one reflects about the correct dissemination of healthcare resources, *justice* develops into an issue. However, it is incomprehensible to grasp why access to expensive medicine for treatable conditions such as a rare disease like Gaucher disease should be centred exclusively around financial concerns. Moreover, having limitations on expensive treatment distribution would place a limitation on further development of orphan medicines which may ultimately lower the cost of treatment (Mavroudis, 2015, p. 1624). “*Rights-based justice*” argues “that a minimum level of health” (Cherry, 2015, p. 56) care is required for everyone (Daniels, 1998, p. 316).

Hughes et al hold “a rights-based approach”, depicting that every person is entitled to appropriate adequate healthcare. This necessitates “that treatment is made available for managing rare diseases” (Hughes D. , 2005, p. 833). Many patients with rare diseases risk not receiving treatment, should access to orphan drugs be denied. The material principle of justice pertains to the theory of justice which we believe in (Beauchamp, 2001, p. 58).

In the health context, the *difference principle* essentially relates to a commitment to reduce health inequalities. Prioritarianism holds that the goodness of an outcome should be related to well-being across all patients, and essentially and importantly in specific to worse-off patients. Prioritarianism could be reasoned in many different ways and the decision of which patient is worst off and deserves health resources over another, can be argued from many different angles and begs other questions, e.g. should patients who are not getting worse currently receive precedence, however, are these patients not particularly at risk to deteriorate? Also, giving absolute priority to the worst off is questionable, when they can only experience marginal gains in health-related quality of life (Brock, 2006, p. 263).

Scanlon et al (1997) embrace a contractualist view of “what we owe to each other” or our obligations or duties towards other people as rational human beings (Scanlon, 1997). He holds that according to various moral theories, individuals should receive priority for treatment based on their *individual* claims to treatment. Brock further suggests that at a minimum, individuals should not be deprived of extremely great health benefits in order to provide many patients smaller health benefits (Brock, 2006, p. 264).

Should a patient with Gaucher disease be denied treatment due to cost constraints, this poses an ethical dilemma related to distributive justice and resource allocation. However, this also affects the autonomy of the individual. Autonomy proposes that it is any person's right to choose "what is in their own best interest" (Teutsch, 2012, p. 2). However, autonomy might be limited if an individual is exercising his or her right but in the process is limiting the rights of others (Teutsch, 2012, p. 2). Though in some instances costly to the healthcare system, healthcare providers desire the liberties to decide what they consider is right and best for their patients' well-being as well as to make autonomous choices without any proscriptions (Graber, 2005, p. 424).

Furthermore, a central precept of public health is the requirement that people with certain diseases undergo treatment whilst a question might arise why high cost, low patient number disease entities like rare diseases may not be receiving the same priorities in terms of resource allocation. These questions, however, cannot be answered without confronting the tension between the interests of the individual and those of the collective. The basic economic problem is how to maximize health and distribute benefits fairly, but still control costs. Powers and Faden are of the notion that the moral justification for health policies depends equally as much on wellbeing, as it does on dimension of health (Beauchamp, 2014, p. 601). Thus, we need to ask the question whether it is morally right to deny a patient treatment when *beneficence* is considered one of the fundamental principles of healthcare ethics and common morality. "*Beneficence*" denotes the notion of actively doing well or being good to others (Beauchamp, 2001, p. 165). This also pertains to making an effort to secure a person's wellbeing and to act in a patient's best interests (Beauchamp, 2001, pp. 43,55). Furthermore, the principle of beneficence is dishonored when a healthcare worker does not have the right to administer treatment to a patient.

This also relates primarily to orphan medicines through the concept of *non-abandonment*. "There is no disease so rare that it does not deserve attention" (Orphanet). "*Non-abandonment*" is the notion that society recognizes the importance of improving the health of patients with rare diseases that are severe and lack alternative treatments (Landman, 1999, p. 224).

More emphasis has been placed on health care because it is required, at some minimum level, for any person to function normally. With diminished health, these members of society no longer have an equal opportunity. This is why a moral compulsion exists to further orphan medicine research and development; without it, a subset of the population's normal functioning and opportunities are restricted.

Gericke et al (2005: 165) argue that should a person be suffering from a rare and detrimental disorder like Gaucher disease with limited availability of treatment, then "society has a moral obligation not to abandon" these patients who have had this "bad luck" or the misfortune (Gericke, 2005, p. 165).

Similar accounts of justice by Dworkin et al argue that people with these disorders should be receiving special priority. Dworkin further holds that it is a fundamental right to "be treated as an equal" (Dworkin, 1977, p. 227). Refusing to treat a person with an expensive to treat condition, should not be an adequate reason to forsake this patient, since it might indicate that we only care about cost-effectiveness and not about human beings as such. The argument which relates to disregarding one patient's life or "forsaking a patient" forms part of an ongoing utilitarianism versus deontological ethics debate. On the one hand, saving several lives versus saving one person and on the other hand the total immorality of killing even one patient and where the end never justifies the means.

In a two-stage Australian survey conducted by Nord et al, a cross-section of individuals were questioned regarding the importance of prioritising cost in the healthcare setting. Results indicated that merely because one disease is more costly to treat versus other illnesses, any patient should not be underprivileged regarding priority for treatment and thus no patient should be discriminated against, even if they were unfortunate enough to suffer from a high-cost disease (Nord, 1995). The authors concluded that the concern with allocative efficiency, as usually envisaged by the economists, is not necessarily always shared by the general public and furthermore, that the cost-effectiveness approach to assigning priorities in health care may be imposing an excessively simple value system upon decision making related to resource allocation.

Linking onto the people born with some or other kind of clinical misfortune, the "*rule of rescue*" proposes a commitment to non-abandonment of individuals with needs for highly specialized treatments, even in resource-constrained settings (McKie, 2003, p. 2407) (Teutsch, 2012, p. 2) (Kling, 2013, p. 95).

The rule of rescue is usually prompted by “identifiable individuals” (such as for instance a “group of trapped miners”) (Kling, 2013, p. 95). If a person’s plight, for instance the ultimate dire consequences of Gaucher disease without treatment, is made noticeable, then people tend to feel more sympathetic towards them.

According to Kling et al an example of a worthy intervention that may be justified by the rule of rescue is when treating Gaucher diseases with enzyme replacement therapy (Kling, 2013, p. 95). Since Gaucher disease causes substantial impairment, Cerezyme enzyme replacement therapy treatment may restore the patient to full function and therefore render the patient fully functional with social capacity as well as a stable economical contributor. Should we abide by moral principles and endeavor to restore a patient’s need for flourishing and reaching full potential, the reasoning of “*equitable rationing*” would entail giving everyone with a rare disease more or less an equal opportunity to have access to life saving “orphan drugs” (Cookson, 2000, p. 329) (Landman, 1999, p. 224).

Rare diseases like Gaucher disease also have immense economic consequences beyond the human toll (Hyry, 2013, p. 1). Individually rare diseases, if not treated, add significant social and financial burdens, concerning entire families, since often family members need to care for family members afflicted with a rare disease and in the process, forfeit employment. However, if patients are treated successfully, it is doubtful whether they would need other additional and sometimes even expensive and even traumatic life-saving treatments and procedures like analgesia and surgery. They may for example further their studies, be employed, earn a decent living and become a key economic contributor and even pay income tax on successful careers. When discussing fair allocation of healthcare resources, we should, however, bear in mind that money spent on one treatment would then be unavailable for another treatment, creating conflict between budgets maximizing the health of the largest part of society (Picavet, 2013, p. 572). It is generally accepted that rationing healthcare might be more challenging than limiting other commodities, because people believe that healthcare is owed to them in principle (Daniels, 1994, p. 27). However, Dworkin et al argue that healthcare should not be compromised “to the detriment of other social goods” (Dworkin, 2000).

The market size of rare diseases is increasing, partly due to the rapid expansion and progress of genetics and partly due to new rare diseases constantly being identified (Juth, 2014, p. 3).

As a rule, when looking at the treatment of rare diseases with scarce resources, and being cognizant of justice in a healthcare system, every person should receive *equal* and “*sufficient of the good*” (Juth, 2014, p. 8). Norman Daniels, an expert on healthcare prioritizations, is of the notion that it is imperative to ensure that any human “reach the level of health *identical to the level of normal species functioning*” (Juth, 2014, p. 8). He believes that any serious disease, regardless of being common or rare, if left untreated, may result in a level far below any suggested level of minimal health. However, unfortunately, medicine for rare diseases are possibly less likely proffered to patients with rare genetic diseases due to their expenses compared to medicines for more common diseases. According to Juth et al the elevated cost and smaller patient pool should, however, not “be a morally relevant factor” in deciding whether a patient needs access to treatment or not (Juth, 2014, p. 6).

Juth et al believe that although “group size can be plausibly considered to be a factor” in terms of morality, he considers “cost or effectiveness” of much higher moral relevance (Juth, 2014, p. 7). Since genetic rare diseases are low prevalence diseases, if each patient is treated, the overall outlay might not be hugely expensive. Also, the same value and consideration that is placed on expenditure towards housing and education, should be placed on the health of all patients. It is argued by some authors that health deserves distinctive priority (Daniels, 1998). I argue that rare diseases also need and deserve more attention. In order to put things further into perspective, let us compare cost efficiency of treating Gaucher disease with some other medicines for non-rare albeit serious diseases like HIV and tuberculosis. Engelhardt further believes that a well-defined, multi-tiered healthcare system constitutes a compromise which benefits most healthcare needs in terms of sound medical practice. This however, needs to be negotiated through open and honest discussion and fashioned to accommodate diverse medical goals.

Scarcity of health care resources will forever remain an inescapable eventuality. Harris is of the notion that while healthcare resources are not unlimited, they are also most definitely “not finite either”, with expansion a clear possibility, making room for increases in budgets or trade-offs against other utilities (Kuhse, 2009, p. 335). In other words, priorities can be renegotiated or reassessed.

In the following chapter (Chapter 3) some suggestions will be made to assist with the difficult decision-making process of resource allocation for a rare disease like Gaucher disease.

The availability of life altering enzyme replacement for Gaucher disease and hence improving quality of life for a patient, brings to the forefront questions about deciding whether the cost of receiving treatment outweighs the disease's detrimental and debilitating consequences. It also asks the question: what would it be like, for me, to be in this patient's position? The answer is simple. Empirical investigations have shown unequivocally "that health is considered to be one of the greatest values in life". (Nordenfelt, 1993, p. 83)

It is therefore particularly evident from the preceding literature that even though treatment might be costly, most patients with Gaucher disease, if untreated, may suffer from various degrees of severely disabling physical and emotional issues. These could have an immense detrimental effect on a patient's quality of life and thus potentially prevent a human from reaching their utmost potential or flourishing. The following section will delve deeper into the ethical dimensions of quality of life (or alternatively phrased happiness).

#### **1.4 Ethical dimensions of happiness or alternatively phrased quality of life for patients with Gaucher disease**

The concept of "*quality of life*" is used to refer to a "state of being" of an individual, particularly portraying a positive or negative deviation from "human flourishing" (Rachels, 2003). In other words, quality of life may depict, amongst others, certain prerequisites with the purpose of becoming (more fully) human.

Many philosophers, including Aristotle, Plato, Bentham, Mill and others, have attested that the best human life is due to happiness. In addition, numerous philosophical theories have been published referring to quality of life as "an account of what makes human life worth living" (Rachels, 2003) (Lea, 2005, p. 234) (Pera, 2011, p. 42).

The three most recognised categories of theories related to *quality of life* are theories of human flourishing, hedonic theories and rational preference theories (Nussbaum, 1993).

Jennings et al hold that holistically, theories of human flourishing attempt to ground our comprehension “of the good life on an account of those functions, capacities, and excellences that make us most completely and entirely human” (Hughes J. , 2003, p. 528) (Jennings, 2002) (Diener, 2006, p. 305). Consequently, flourishing as a human being, is not only the extent to which “we attain and master those capacities”, but also the extent to which “we avoid those conditions” that would impede “those capacities” (Jennings, 2002). Conversely, hedonic theories identify quality of life explicitly with happiness or pleasure.

Finally, quality of life with reference to “actual satisfaction” or realisation “of a person’s rational desires or preferences” is depicted by rational preference theories (Jennings, 2002). According to Jennings et al, all these theories are controversial in nature. Yet, despite its ambiguity, the concept of quality of life remains essential, particularly in the sphere “of health care and social services” (Jennings, 2002). The concept of quality of life closely parallels the notion of happiness and involves our entire existence. Constanza et al believe that quality of life “is a multidimensional construct emerging from the evaluation of multiple needs” and obviously, “each need is assumed to contribute in varying degrees to overall” quality of life of the individual (Constanza, 2007, p. 272).

Ancient Greek history depicts various different definitions of happiness and in addition the ability of a person to reach his or her utmost potential (McMahon, 2006). Plato’s notion of a happy life was that it must satisfy at least three conditions. The Nicomachean ethics teaches us that life must be desirable for its own sake, sufficient of itself to satisfy us and it must be the life that a wise man would prefer to any other life (Aristotle, 384–322 B.C.). According to Aristotle (384 B.C. – 322 B.C.) the best life is one filled with *happiness* or “*Eudaimonia*”. Thus, Aristotle believed that “happiness is the highest good and the end to which all our activities ultimately should aim” (Thomson, 2004). Aristotle’s notion of happiness mainly rests on ourselves, and encompasses our life in entirety. Aristotle further held that there are three kinds of contingencies that can affect our happiness, namely pleasure, wealth and honour. These encompass eventualities during our birth and life and even after our life. (Thomson, 2004)

Importantly, if we are suffering from a lack of health or deterred from optimal functioning because of illness, we cannot live a fulfilled life of satisfaction. If a patient is forced to endure continuous pain, such as the debilitating bone pain of a patient with Gaucher disease, reaching full potential may be somewhat more challenging.

Aristotle believed a worthwhile definition of human well-being and hence *happiness* is to live an active, worthwhile and complete life. Added to this, for Aristotle, a complete life shows that potential not crowned by accomplishment is not enough to consider an individual's life exultant and content. Thus, the virtue or excellence of a man is if he can live his own life to the *utmost of his ability and potential* (Taylor, 1955, p. 91). The ultimate happiness for Aristotle is to obtain a virtuous character. A person lacking health and wellness will experience less wellbeing as well as worsening of emotional and physical welfare. Thus, unquestionably, a Gaucher patient with bone complications might experience reduced quality of life and therefore less happiness, which might even ultimately lead to a negative social impact and potentially a reduction in economic earning potential (Belmatoug, 2012)

Aristotle's "activity-oriented theory of the good life" has apparently not excessively affected present-day welfare philosophers. Generally, a broad-based utilitarian approach seems to be the overwhelming preference. It seems as if a moral rationalization for withholding funding to specific medicine is certainly lacking, bar the excuse of lack of resources to fund a wide spectrum of disease entities. As previously alluded to, according to the great utilitarian philosopher, Jeremy Bentham (1784-1832), "individual human happiness consists of achieving a greater balance of pleasure over pain for the greatest number of people" (Stangroom, 2012, p. 84).

However, this can only be done if there is a distinct way of comparing pleasures with pleasures and pains with pains and pleasures with pain (Stangroom, 2012, p. 84). Keeping in mind that concurring with Bentham's principle of utility, this obviously refers to the notion of increasing happiness or satisfaction in a person or a group people. Bentham's notion revolves around an action which must either be based on an aspiration for pleasure or a craving to avoid pain, differentiating Bentham as a representative of the school of *psychological hedonism* (Nordenfelt, 1993, p. 24).



Bentham's practical solution to compare pain and pleasure in different situations, was a kind of "hedonistic calculus" which he claims will not only quantify pleasure, but also offers a system for its qualification, measuring amongst others, pleasure's duration, intensity, purity, certainty, fecundity and extent. He also considers the demerits of different kinds of pain and admits that pleasure and pains are relative to the perceiver and their education, religion and social standing. Thus, according to Bentham, we must "sum up all the values of the pleasures on the one side, and those of the pains on the other" (Nordenfelt, 1993, p. 24). Should the balance lean predominantly towards the pleasure side, this will obviously indicate satisfaction.

Utilitarians believe that not only does the morality of the action *solely* matter on the *consequences* of the action, but that the actions matter only as long as they involve the greater/lesser happiness of individuals. They further believe that each individual's happiness should get equal consideration. According to Rachels et al, "happiness is the only thing desirable as an *end*, whilst all other things being only desirable as a means" (Rachels, 2003, p. 114). For utilitarians, happiness is pleasure. They identify happiness/pleasure generally to include all mental states that feel good. This concurs somewhat with the hedonistic school of thought, which focuses on elements of pleasure and pain. However, the main notion of utilitarianism is irreconcilable with the ideal of justice. According to the notion of utilitarianism, deeds are justified if happiness largely surpasses unhappiness even by repudiating the rights of people in the process, purely because this practice results in good results for the most people or society at large. Thus, seemingly for utilitarians the pleasure of the majority clearly outweighs the suffering of the one.

Thus, if we carefully reflect on the ethical reasoning behind "Bentham's principle of utility" (Rachels, 2003), it suggests that actions promoting or decreasing pleasure or happiness of a person or a group of persons should be assessed and that we should ultimately abstain from actions which do not have the same good consequences for *society as a whole*. In other words, utilitarianism depicts the notion that acts are considered to be right only if they "produce the greatest happiness for *the greatest number of people*" (Rachels, 2003).

Therefore, there is no place for individual rights in utilitarianism and this notion thus limits treatment of the individual, regardless of the good accomplished. However, should we not rather endeavour to examine each patient's case on an *individual* basis, acknowledging that each patient has an inherent right to a happy and fulfilled quality of life in order to realise their individual potential? Even though seemingly impossible to articulate the deepest dimensions of life, we somehow need to optimise and harness each *individual's* potential to enable them to live a full, good and happy life. Optimal treatment to enhance a patients' quality of life may certainly be a step in the right direction.

Harris et al describe the degree of need for healthcare as the importance, urgency or intensity of need, together with the amount of that which is vital and ultimately "the capacity of benefit" derived from fulfilling an individual patient's need (Kuhse, 2009, p. 336). Fulfillment of need could, however, further be described in terms of duration of satisfaction once the need is fulfilled, as well as the patient's capacity to benefit from the supply to satisfy his/her need. The intricacy is to decide which of the previous dimensions implore greater necessity for treatment to make resource allocation more compelling for one treatment over another. One important dimension of this equation is to reflect on what a patient stands to lose if left untreated. What would the influence be on quality of life of a patient or how does one optimally assess the lack of quality of life? Assessment of loss of quality of life should definitely comprise of a multidimensional approach, taking into consideration numerous measures (Nussbaum, 1993). It should be evaluated on an individual basis rather than with a multi-focused utilitarian approach, which takes into consideration happiness for the greatest number of people versus happiness for an individual.

Morally speaking, so long as the quality of life is worth having for the person who is living the life, people's lives and fundamental welfares should essentially receive equivalent ratings, irrespective of life expectancy, quality of life, age and other differentiating factors. Treat equals as equals. Although diseases each have a clinical component, judgment can clearly not only be made on one single dimension, but should be based on a fair and equitable assessment of all known and relevant facts. Harris believes that each life should be counted as one. No more and no less (Kuhse, 2009, p. 348). Each individual, including a patient with Gaucher disease, is a moral entity with equal moral worth.

Compared with any other person, each patient with Gaucher disease should be offered a realistic and reasonable chance to receive treatment. Justice and fairness entail that we should at least endeavour to present an individual the possibility of prosperous living and happiness.

Analogous to other rare diseases, Gaucher disease, if diagnosed at all, is often diagnosed long after symptoms have appeared (Mistry, 2007, p. 697). A delay in diagnosis carries immense costs, not only by preventing an individual from receiving timely treatment and thus suffering from unnecessary long-term detrimental side-effects, but also by increasing time spent on the exhausting odyssey of multiple diagnostic tests (Weinreb N. , 2008, p. 890). Genetic testing may afford these patients an equal opportunity to attain their full capability as human beings. The next section will address the importance of genetic testing of rare diseases and the ethical issues associated with this rapidly emerging field.

## **2. Genetics**

### **2.1 Genetic diseases and the advent of genetic testing**

Scientific technology has brought about immense advances in human prosperity, including genetics, determination of DNA and the possibility of prediction of inheriting a rare genetic disease (Economist, The effect of today's technology on tomorrow's jobs will be immense—and no country is ready for it, 2014). “Watson and Crick”, who “discovered the existence of DNA in 1953” (Portin, 2014, p. 293), count amongst some of the most famous men in modern biology and were rightly, rewarded a Nobel Prize for the immensity of their discovery (Portin, 2014, p. 293).

Genetic science and genetic engineering today present us with immeasurable opportunities and possibilities (Rosen, 2011). It has revolutionised not only the ways in which we seek to understand the world and ourselves, but also our attempts to change the world (by engineering outcomes barely conceivable until now). In the modern era of genetic medicine, there exists the possibility of access to a novel kind of knowledge pertaining to our own micro-cosmos of genes. This new opportunity provides the prospect to know about future harm or detriment that may come to you or your blood relations in the form a genetic disease like Gaucher disease (Aber, 1998, pp. 77-95) (Berry, 2007, pp. 1-4).

Although genetic testing (determination of some genetic factor in an individual) and genetic screening (to ascertain prevalence of some genetic factor in a population or population group, usually as part of a public health program) have numerous ethical issues in common, they are different in scope (Chadwick, 2008, p. 160). Both of these procedures are linked with particular sensitivities, especially in light of the history of genetics and its abuse in eugenics (Chadwick, 2008, p. 160).

## **2.2 Genetic testing, disclosure of genetic information and autonomy**

Genetic testing, although somewhat novel, has made huge advances in the scientific domain during the past few years. Advancing knowledge of genetic disorders like Gaucher disease has created a host of ethical and social dilemmas associated with genetics (Gross, 2002, p. 151) (Beutler, 1993, p. 5384). For instance, individuals subjected to genetic testing have created considerable debate especially pertaining to ethical and moral concerns (Borry, 2008, p. 139). As soon as an individual is classified either through family history and/or clinical signs and symptoms as having a genetic disorder, their chance of developing the disease may be elucidated by undergoing a genetic testing procedure. The decision to undergo a genetic test is based on autonomy and is a choice that each person needs to make by him/herself. This should, however, be based on an informed decision. In children, genetic testing for conditions that will only show symptoms in adulthood, like type 1 Gaucher disease, it is advised that the decision to test should be postponed until adulthood, to ensure that the decision is made maturely.

Where familial genetic disease is common, parents may ask for genetic testing in children. These requests might create a predicament for paediatricians. Testing of some adult-onset diseases may show benefit in childhood because of early detection and treatment or alternatively, a negative test result may bring comfort and relief to the parents (Charlisse, 2012, p. 163). If no medical cure or medical benefit is available for a disease that will only develop in adulthood, the international genetic society guidelines recommend not to test based on the notion that a child has a right to autonomy.

This also eliminates the decision to be made in adulthood (Malpas, 2005, p. 273). Each individual can base the decision on their moral beliefs and preferences. They can decline or give consent to the genetic test being done. Before decisions to test are made, all relevant information about the desired and possible outcomes of the test and likely choices that might arise, must be considered. Only test children if the goal is to improve medical care (CanadianPaediatricSociety, 2003, p. 42)

Parents and families, as well as the affected individual with the rare disease often feel overwhelmed by all the medical details. They need counselling to understand the genetic and familial implications of genetic contributions of the disease as well as future inheritance patterns and the impact on future pregnancies. Therefore, psychosocial support is pivotal in addressing fears and rationalisation in order for patients and family members to make sense of their situation (Glass, 2016). Genetic counsellors therefore play a pivotal educational and information-imparting role as well as an emotionally and practically supporting role. In this way, people can make their own decisions based on their beliefs and wishes that are firmly grounded in biological reality (Kuhse, 2009, p. 245).

Since genetic information can clearly be correlated to a person's identity, it is considered confidential. The receipt of diagnostic information changes patients' ethical responsibilities and their understanding of their own ethical position (Aber, 1998, p. 84). Numerous ethical questions may arise from genetic testing. A person's DNA is unique, excluding identical twins. However, simultaneously, relatives or unknown relatives may discover undisclosed genetic information about themselves, should previously unknown knowledge of genetic information about a certain individual be made public (Durfy, 2001) .

“Privacy and confidentiality of genetic information present perplexing and challenging issues that could result in devastating effects for individuals, families, community and society” (Lea, 2005, p. 236) (ACOG, 2008 (Reaffirmed 2014)). Some examples of these issues include amongst others, breaking physician-patient confidentiality by sharing private health information (e.g. genetics) about the patient to third parties without the patient's consent.

This may not only detrimentally affect future relationships with other potentially affected family members, but may also lead to discrimination by for instance health insurers.

Patient and social welfare necessitate rules of confidentiality based on the well-known principles of privacy and respect for autonomy. Individuals' decisions to control access to information about them should be respected. If the patient refrains from passing on the relevant information to family members, the question arises whether the genetic counsellor may justifiably break confidentiality under the circumstances? Serious problems could ensue, should private and personal information be divulged through a family network contrary to the family's wishes. Inadvertent disclosure of information about a patient's condition or genetic predisposition to other members is a hazard and must be guarded against at all cost (Kuhse, 2009, p. 246). People may also fear that genetic screening will lead to the family making choices related to procreation, focused on the genetics of the child. The community and society may, also often not understand the consequences of the rare disease, often because of lack of awareness. By having a diagnostic label, genetic discrimination in health insurance or even societal stigmatisation could occur (Durfy, 2001).

To preserve the principle of non-maleficence (to do no harm) and the principle of beneficence (to do good), a careful assessment of risks and benefits is necessary. According to Lea et al the principles of non-maleficence and beneficence similarly relate to the choice to undergo genetic testing which might uncover previously unknown genetic information about a pregnant mother and her offspring (Lea, 2005, p. 236). The clinician should always point out uses and limitations of a test in order to comply with adequate informed consent procedures. In Mrs. X's case, this would include conversing with her in the language she is most comfortable with to provide proper information and a balanced view of potential benefits and harms in order to make a proper informed choice.

However, one should still be cognizant of the fact that knowing the probability of inheriting a gene mutation does not necessarily lead to an explanation of the severity of the condition ("variable expression"), or explicit presence at all ("variable penetrance"). However, globally there is a move towards expansion of prenatal testing (Ross, 2008, p. 104). Some background on the genetics of Gaucher disease will elucidate associated concomitant ethical dilemmas.

When someone like Mrs. X is afflicted with a genetic heritable condition, the whole family is involved. Hence, although difficult, it is still imperative that the risk between relatives is clearly communicated. However, many aspects influence decisions of disclosure of information, even within a closely knit family group (Gallo, 2009, p. 65). According to Gallo et al, the most often encountered motives reported for revelation of information to family members or relatives comprise an apparent obligation, need or responsibility towards for instance her partner to disclose (Gallo, 2009, p. 65) (Forrest, 2003). These women are thus faced with an important balancing act between responsibility and autonomy: whether to give information which might negatively influence future lives versus regard for others “having a right to information which may facilitate their future health management decisions” (Hallowell, 2003, p. 75).

Thus, additional ethical questions, regarding genetic screening may arise from the case study of Mrs. X: Should the partner/spouse (biological father) of the pregnant patient (diagnosed with Gaucher disease) also be tested for Gaucher disease? In this instance, Mrs. X has Gaucher disease. If her partner is a carrier of Gaucher disease, chances that the baby also has the disease is vastly increased, in actual fact almost 50% (Refer to Figure 1 “Inheriting Gaucher Disease”).

However, the partner/spouse has a right to privacy and might not necessarily want to consent to genetic testing. Protection of privacy of the results may result in other family members being unaware of their own risk (ACOG, 2008 (Reaffirmed 2014)). Thus, one of the other burning issues that a patient with Gaucher disease also needs to reflect on is disclosure of genetic information (Borry, 2008, p. 139).

The dilemmas of disclosure of genetic traits to a spouse or partner are intensely personal and confront both patients and carriers (regardless of known or potential carriers of genetic disease). In the case study, Mrs. X faces the challenge of whether disclosure is obligatory or not. A partner consummating marriage with the intent on raising a family may insist on open disclosure, which in turn “creates an obligation to seek genetic information and a duty to” divulge this “information to prospective” partners (Gross, 2002, p. 152).

By testing both Mrs. X and her partner for Gaucher disease, a physician can now ensure early treatment with enzyme replacement therapy for both the pregnant mother and, if necessary, also to her partner. This could allow them the possibility of a considerable increase of current quality of life and hence assist them to live a longer, and socially as well as economically, a more productive life (Weinreb N. , 2002, p. 112) (Hayes, 1998, p. 521) (Masek, 1999, p. 263).

Respect for patient autonomy is important (Gillon, 2003, p. 307) (Varelius, 2006, p. 377) (Beauchamp, 2001, p. 176). The “principle of respect for autonomy” is most commonly associated with “enabling patients to make their own decisions about which” health care “interventions they will or will not receive” (Beauchamp, 2001, p. 176). In addition, the notion of autonomy further changes dramatically during a pregnancy scenario which requires a careful balancing act weighing between the actual physical risks to the pregnant woman versus potential benefits or harms for her foetus. Post-partum this balance shifts to weigh the child’s interests against the psychological, spiritual or economic interests of the child’s family (Lantos, 2008, p. 95). The decision to undergo a genetic test is based on *autonomy* and is a choice that each person needs to make. This should, however, be based on an informed decision (Lea, 2005, p. 234). The “importance of autonomy in decisions about reproduction and genetic testing is” emphasized “in modern bioethics” (Kuhse, 2009, p. 246). This emphasis on autonomy is particularly demonstrated through the pivotal importance of informed decision making and consent pertaining to healthcare.

According to Hildt et al, autonomy incorporates multiple “aspects such as self-determination, free decision-making, and self-creation” (Hildt, 2009, p. 143). A fundamental part of autonomy is an individual’s capability to contemplate his or her values and partialities and thus to shape his or her existence correspondingly (Hildt, 2009, p. 143). Autonomous decision-making for a patient involves sufficient access to health-related information so that he/she can decide at will and in the absence of external constraints on the further course of treatment (Hildt, 2009, p. 143). The “impact of the information obtained in predictive genetic testing” as opposed to informed-consent related situations on individual autonomy is however multifaceted and “much less defined”, since repercussions of the genetic test results on for instance the individual’s future as well as individual preferences have to be carefully considered (Hildt, 2009, p. 144).



In an effort to uphold their obligations of care and yet preserve autonomy, genetic screening forces women to adopt different strategies. For an individual, by applying autonomy, you actuate the direction and continuity of your life plans and accept accountability for your actions/decisions. Paramount to autonomy, an individual should have the ability to know what he or she prefers, aligning this to his or her values and to subsequently change his or her life accordingly. Individual autonomy is important when referring to genetic testing. One should ideally not only concentrate on medical treatment, however, all options and measures to prevent the effect that the test results will have on future lifestyle choices, personal beliefs and long-term desires should be taken into consideration. Additionally, options that include the freedom to make informed decisions as well as realising the impact of the decision on future lifestyle, family, society and religious conditions in your personal sphere should be taken into consideration (Hildt, 2009, p. 143).

In order to delve deeper into an ethical appraisal of genetic screening for Gaucher disease, it is important to provide an overview of what this practice entails. As soon as an individual is classified either through genetic inheritance and/or clinical signs and symptoms at risk for a genetic disorder, their predisposition to develop the disorder may be elucidated through genetic testing. The capability of researchers to investigate through genetic screening processes for particular genetic irregularities and malformations has directed researchers to three instances in which the ethics of genetic screening are clearly elucidated: embryo, neonatal and fetal screening, as well as carrier screening, and testing for economic reasons. Pertinent to this particular case study and thesis, is pre-natal screening and carrier screening, hence the following discussion will deal mostly with those.

The possibility of being a carrier for certain genetic defects, are elucidated through carrier screening. This will clarify to prospective parents the likelihood of both or either of the parents being a carrier for a particular genetic defect. “Carrier screening can reduce the burden of genetic disease, especially in populations at risk” (Rosner, 2009, p. 8.6) (Vallance, 2003, p. 473). Ideally, carrier screening is performed pre-conception because this allows for greater decision-making latitude (Ross, 2008, p. 104).

A study by Borry et al raised some difficult questions regarding the appropriateness of a “carrier screening” program “for type 1 Gaucher disease” (Borry, 2008, p. 139). There is convincing evidence versus carrier screening for Gaucher disease since the disease course is highly variable (Rosenbaum, 2015, p. 549). However, affected patients can, with screening identification and early diagnosis, be effectively treated with enzyme replacement therapy (Weinreb N. , 2002, p. 112). Generally speaking, *autonomy* or “the right to know” is considered pivotal “to situations in which appropriate preventive or therapeutic measures can be taken, or to those in which the result is relevant to family planning decisions” (Hildt, 2009, p. 146).

The principle of autonomy particularly regarding predictive genetic testing is of fundamental significance as to deciding whether to undergo predictive genetic testing. However, it is equally relevant to gain knowledge and insight which might possibly influence an individual’s life in future (Hildt, 2009, p. 147). In the Case study of Mrs. X, a further argument can be made that genetic screening may well afford couples with knowledge and control. This is confirmed by Zuckerman et al who stated that genetic screening will “allow couples at risk to be identified and to make an informed choice” (Zuckerman, 2007, p. 1290). Genetic screening provides parents with the desire to reproduce with useful, although limited information regarding the possibility of a genetic defect of an offspring. The limitations of genetic screening are that these tests can often not accurately predict if the affected individual will present with symptoms of the disease, the severity of the symptoms of the disease, or disease outcome. Genetic test results may be inconclusive in ultimately determining a patient’s risk.

It may also afford couples the opportunity to decide not to procreate, to adopt a child or to go through a process of *in vitro* fertilization (IVF). They may even decide, after careful consideration, to screen embryos or to abort the affected fetus after discovering that they both are carriers of a recessive genetic defect like Gaucher disease.

In view of particular results, certain individuals may make “involuntary” decisions, such as “abandoning certain valued pursuits” or feeling unable to make choices like deciding not to procreate (Hildt, 2009, p. 148).

According to Hildt et al, the individual, left with a substantial reduction in existing options, may hence be forced to make “inauthentic choices”, resulting in a substantial limitation of “individual autonomy” (Hildt, 2009, p. 148). In order to curtail anxiety associated with choice and responsibility, an individual might sometimes make a decision underpinned by sociocultural influences, such as peer pressure. Thus, the person might not be properly appraising universal, personal and holistic implications, but prevailing to norms in the decision-making process. Thus, by making the comfortable decision and failing to recognise that there is indeed a huge variety of choices available, the person may be compromising their individual autonomy.

One of the natural instincts of most couples is to conceive flawless children free from the burden of any disorder. This has led to the advent of embryo, neonatal and fetal screening in the womb which has “been designed to identify infants with severe disorders that are relatively prevalent and treatable (or controllable)” (Dhondt, 2010, p. S211). Newborn screening (NBS) is a population-based program that seeks to screen newborn babies for early-onset, treatable disorders (Ross, 2008, p. 105). Prenatal testing involves a number of different tests including genetic carrier testing, “ultrasound, amniocentesis or chorionic villus sampling (CVS) or preimplantation genetic diagnosis” (Ross, 2008, p. 104).

Especially in Western society, pre-natal screening for genetic impairment is progressively considered as a regular practice (Press, 1997, p. 980). Early detection of Gaucher disease is vital for both patients and their relatives and represents justification for instituting NBS (Wang, 2011, p. 459). It is also clear that earlier initiation of therapy can make a substantial difference in the outcome of the disease progression (Wang, 2011). In the United States, every newborn partakes in NBS for at least twenty-nine disorders, where evidence suggests that early detection is possible and beneficial (Matern, 2015, p. 206).

Lisi et al conducted thirty-eight telephonic interviews with genetic healthcare providers to investigate whether NBS of lysosomal storage diseases (LSDs) were appropriate (Lisi, 2016, p. 373). Results indicated that amongst the “LSDs discussed, Pompe was considered most appropriate” for NBS and “Krabbe least appropriate”, whilst Fabry and Gaucher disease were viewed less favourably due to later onset of disease (Lisi, 2016, p. 373).

It seems that the main argument against genetic screening is that as humans, we are not privy to universal knowledge (Thompson, 1999, p. 263). However, the universal truth is that genetic screening seems to be accepted as a norm in society today. The use of pre-natal testing has thus become accepted over the past 20 years (Thompson, 1999, p. 263). Expanded programs raised novel ethical questions. One of the arguments against screening is the risk of discrimination or stigmatization (De Montalembert, 2005, p. 528). Some individuals might think that genetic screening may confer unfair discrimination on those individual persons who might be perceived as possessing “inferior” genes.

Parents may also experience anxiety resulting from a false positive test or residual “anxiety about the current health of their carrier child and their future reproductive decision making” (Duff, 2008) (Lewis, 2006, p. 533), respect for autonomy of individuals to come to their own conclusions about choices, as well as apprehensions about medicalization during the neonatal period (Dhondt, 2010, p. S215). “Couples whose older children were born before screening may also become anxious regarding their up-to-now” healthy children (Zuckerman, 2007, p. 1282). Unanticipated medical tests and evaluations may be conducted on adults with asymptomatic Gaucher disease who have now been identified through screening (Zuckerman, 2007, p. 1282). Chadwick et al held that in addition to creating uncertainty and anxiety, some patients might also experience low self-esteem (Chadwick, 1997, p. 13).

Some authors like Takala et al suggest that an individual is personally responsible to obtain all relevant information through genetic screening and to decide whether the benefits of gathering this information outweighs the risks (Takala, 2000, p. 171).

## **2.4 Genetic screening and ethical theory**

Rhodes et al propose that in order to advance society’s knowledge of population genetics, carriers of rare genetic diseases are obliged to undergo genetic screening (Rhodes, 1998, p. 23). Data from both carriers and non-carriers are imperative in this instance and societal benefit clearly outweighs the disadvantages to any individual, which is in support of *utilitarianism*.

In the example of prediction of familial hypercholesterolemia in a susceptible population, preventative measures instilled earlier may lead to pro-active lifestyle and dietary changes including incorporating other holistic measures. Knowledge of a predisposition may prevent or ameliorate some of the consequences of the future disease and allow the affected society to make informed choices timeously.

Historically, utilitarianism, which was initially proposed by David Hume and later on firmly established by both Jeremy Bentham and John Stuart Mill describes the moral goodness of actions by their consequences (Lea, 2005, p. 234) (Pera, 2011, p. 42) (Rachels, 2003). According to these philosophers, the acts considered to be right “produce the greatest happiness for the greatest number of people” (Rachels, 2003). Utilitarianism was developed in England during the Enlightenment Era, more or less at the time of the Industrial Revolution, by the eccentric lawyer, “philosopher and social reformer Jeremy Bentham (1748-1832)” (Rachels, 2003). Bentham was specifically interested in social and political reform, most notably in criminal law. Bentham already formulated his principle of utility as early as 1780; however, his theoretical basis for utilitarianism was only published in 1789 in his “*Introduction to the Principles of Morals and Legislation*” (Rachels, 2003). Applied to genetics and subsequently a rare genetic disease like Gaucher disease, utilitarianism broadly supports genetic testing, genetic selection, gene therapy and genetic enhancement of offspring, aiming at enhancing the opportunity of such individuals to enjoy the best lives, but also to lessen the burden on society (Fulda, 2006, p. 145).

Prior knowledge of a genetic disease and prevention of parents unknowingly passing on the genetic disorder by not having children may lessen the burden on society that often needs to pay high costs for expensive treatments (Fulda, 2006, p. 145). Through genetic testing and screening and notifying at risk family members may not only delay onset of symptoms through early medical intervention but may also decrease the *duration* and extent of symptoms (Fulda, 2006). Furthermore, through sufficient preparation and appropriate lifestyle changes this may impact on the quality of life. By allowing family members to undergo genetic screening and to make informed choices that may influence the future of their families, the knowledge could also enable them to make informed decisions about “passing on the genetic defect” (Fulda, 2006, p. 145).

The moral theory of utilitarianism yields a principle (*beneficence*), with the following rule in mind: net aggregate of good for the majority of persons, with a total result of absolutely minimal suffering. The principle of beneficence rests on actions done to promote only good and well-being of others. Utilitarianism states that under any given circumstances, “*we should do what will have the best overall consequences for everyone concerned*” (Kuhse, 2009, p. 15). Thus, for utilitarians, the ultimate moral principle is the *principle of utility*, which is all about pleasure and satisfaction of human needs. This sounds great, since almost everyone would agree that well-being is most certainly a primary end goal for any individual on earth. In contrast with Kantianism, utilitarianism is not about pleasing God or being faithful to abstract rules. Utilitarianism is all about making the world as happy and content as possible.

Bentham held that since human beings essentially are primarily pain-pleasure organisms, morality and political philosophy should thus hinge on minimizing pain. So, any action is good if it leads to human happiness and bad if it interferes with the happiness of others. Could one thus venture to ask the question: what is happiness? And how can it be quantified or measured? Doesn't happiness mean different things to different people? Or are there even different degrees of happiness? Bentham believed that one should ultimately ensure “*the greatest amount of happiness to the greatest number of people*”. Thus, in the end with utilitarianism, the *consequences* or most importantly, the *absolute best outcome for the most people involved*, are what matters most.

John Mill believed that utilitarianism should ultimately focus on general happiness, regardless of whether this will increase one's own happiness, thus, closely linking utilitarianism with the ethics of Christianity and altruism (Paley, 1785, p. 56). Interestingly, Nietzsche on the other hand criticized utilitarianism by querying “the psychological possibility of the sort of disinterested altruism he perceived that utilitarians endorse” (Anomaly, 2005, p. 5).

Since the first origin of Bentham's theory, a few different branches of utilitarianism have evolved, namely “*act utilitarianism*” (by direct appeal to the utility principle it disregards rules and justifies actions), *rule utilitarianism* (considering consequences of adopting certain rules), *negative utilitarianism* (morally right and wrong actions depend solely on the consequences for total well-being) and *two-level utilitarianism* (moral decisions primarily based on intuitive moral rules except in rare instances where critical reasoning is involved).

These different branches use different approaches to maximize happiness and pleasure. However, the underlying principle remains the same. Happiness for the majority reigns supreme. Perhaps a few questions might arise concerning the universal applicability of Utilitarianism. Although happiness seems to be universal, the theoretical model of Utilitarianism seems to be more applicable for public policy than to clinical medical ethics and that barring the very good intentions of utilitarianism the practical case-by-case implementation in each and every instance may be fraught with difficulty. Average utilitarianism depicts choosing the act that capitalises on utility (individual good) *per individual*; aggregate utilitarianism says select the act that augments the totality of utility *across individuals*.

An argument can also be made that genetic screening could assist by increasing the future prospects of Gaucher disease patients if timeously identified and diagnosed. This may have a major impact on the potential of the individual with regards to their participation in the family and in the community. Buchanan et al hold that “protecting normal biological functioning is not an end in itself” (Buchanan, 2000, p. 81). When we preserve people’s normal functioning, this maintains their ability to participate and contribute to “social, political, and economic life” (Buchanan, 2000). Fully functioning individuals can also totally participate and compete as normal citizens in all domains of social life (Buchanan, 2000). Persad et al even hold that resource allocation might be dependent on *usefulness* of a person (Persad, 2009, p. 423). This means that reflection might be given to awarding resources on the basis of future usefulness of a person and on whose “continued existence is clearly required.” Thus, if properly treated patients with Gaucher disease can make a significant social and economic contribution, closely linking the greater societal benefit to utilitarianism.

Conversely, however, genetic screening can also bring about some other potential ethical dilemmas, for instance the possibility of data mining of genetic information (especially those with hereditary diseases) could pose “an underlying threat to medical and health-related privacy” (Andrews, 1994).

It is apparent that based on a “rights-based moral theory”, that every individual has particular “moral or natural rights” (Breakey, 2015). This includes, amongst others, the right to life and the right to privacy. “Rights based theories” comprise “entitlement” as well as “positive rights” which assert that we are entitled to particular rights for example, healthcare (Breakey, 2015). Negative rights are also included, which impart “the freedom to do something without interference from others” like, for instance “the abuse of genetic information” by third parties might interfere with individuals’ rights to keep medical information private and it also intervenes with an individual’s “rights to apply for jobs that have reasonable insurance coverage” (Breakey, 2015).

Should Mrs. X for instance apply for a job, the underlying threat of Gaucher disease detrimentally influencing her health and wellbeing, might count against her in being successful in her application in obtaining the position, even though this is directly against government policy and infringing on her human rights. Some employers might also suffer from “genetic fatalism” which gives them a grossly exaggerated view of genetic outcomes. “Genetic fatalism” is associated with the belief that genetic outcomes is *determined*, and above all, *fixed* and *unchangeable*. Thus, employers might have the same (somewhat misguided belief) like Watson, “quoted in Time Magazine” (Jaroff, 1989, p. 62).

*"We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes"* (Jaroff, 1989, p. 62) (Alper, 1993, pp. 511, 513). Employers may overlook hiring a potential job contender with “a genetic link to” Gaucher disease, despite that individual’s potential performance value (Guttmacher, 2003, p. 562). This is notwithstanding the fact that for patients with type 1 Gaucher disease, the clinical course and life expectancy are extremely “variable, encompassing a spectrum ranging from” wide-ranging “disease presenting early in childhood to” an indolent or sometimes “asymptomatic disorder discovered unexpectedly in elderly adults” (Rosenbaum, 2015). Also, as mentioned before, successful treatment with enzyme replacement therapy should enable a Gaucher patient to have a complete and fulfilled life, thus assisting him or her to reaching his or her full potential as an individual, and making a meaningful contribution to society (Masek, 1999, p. 263) (Weinreb N. , 2002, p. 112) (Hayes, 1998, p. 521).



Genetic testing may supply insurance companies and employers the ability to screen people to determine their dispositions for certain diseases. This could lead to inflated premiums and discrimination. Insurance companies will most probably also be more averse to accept a patient with Gaucher disease or even an individual with the probability of inheriting the disease genetically. Insurance rates might be increased dramatically or coverage might be denied altogether (Guttmacher, 2003, p. 562). Therefore, a breach in confidentiality regarding the results of genetic screening information may directly violate the rights of affected individuals (ACOG, 2008 (Reaffirmed 2014), p. 6). This kind of discrimination against individuals directly opposes Rawls' theory of justice which particularly underscores justice and fairness of a democratic and free society, thereby ensuring *equality* for all citizens regardless of their situation (Boldt, 2011, p. 216).

Genetic screening may not give exact information since the disease course of Gaucher type 1 disease could be unpredictable. Because genetic testing may not supply sufficiently comprehensive information to a patient and the family, these tests may consequently necessitate complex moral decision making. This can lead to uncertainties for both physicians and patients.

For parents like Mrs. X and her husband, this situation could create an “ethical dilemma” entailing the difficult choice of whether “to continue or end the pregnancy without having proper knowledge of the severity of the disorder” (Lea, 2005, p. 238). This will be further addressed in the next session.

### **3. Abortion**

#### **3.1 Abortion on medical grounds and ethical theory**

Another possible ethical dilemma could be whether, depending on the disease severity, the baby should be aborted or not.

In the fictional case study described in Chapter 1, Mrs. X has been diagnosed with Gaucher disease and the biological father, after proper counselling and informed consent procedures were followed, was subsequently tested and found to be a carrier for Gaucher disease.

Thus, the likelihood of the baby affected with Gaucher disease is extremely high – 50%. The family thus has to decide whether abortion should be weighed as an option (refer to figure 1 in Chapter 1: “Inheriting Gaucher Disease”).

Gaucher disease can be diagnosed as early as between Week 18 and 20 of gestation. This is the time period where the embryo grows into a fetus (non-viable) and late-term (viable). This is border line on whether maternal discretion or the fetus’ best interest must be used as a determining factor to decide to terminate the pregnancy. In South Africa, the “Choice of Termination of Pregnancy Act (Act 92 of 1996)” is extremely liberal. This act declares that in South Africa, “any woman of any age can get an abortion by simply requesting with no reasons given if she is less than 13 weeks pregnant. If she is between 13 and 20 weeks pregnant, she can get the abortion if (a) her own physical or mental health is at stake, (b) the baby will have severe mental or physical abnormalities, (c) she is pregnant because of incest, (d) she is pregnant because of rape, or (e) she is of the personal opinion that her economic or social situation is sufficient reason for the termination of pregnancy. If she is more than 20 weeks pregnant, she can get the abortion only if the mother or the fetus' life is in danger or there are likely to be serious birth defects” (GovernmentGazette, 2008). Furthermore, the South African Constitution underscores every citizen’s human right. In fact, the “Bill of Rights” states: "Everyone has the right to bodily and psychological integrity, which includes the right [...] to make decisions concerning reproduction," though section 27(1)(a) declares that "Everyone has the right to have access to [...] health care services, including reproductive health care."

Giannubilo et al hold that “signs and symptoms of Gaucher disease may have” a possible detrimental influence on both “pregnancy and birth” (Giannubilo, 2015, p. 54). In particular, massive hepatosplenomegaly may alter normal growth of a fetus during pregnancy. In addition, complications exacerbated during pregnancy, including anaemia and thrombocytopenia may unfavourably influence the patient’s haemostatic profile and even increase the patient’s bleeding tendency. This may become critical during birth. The author mentions that pregnancy may also adversely “affect the course of Gaucher disease” (Giannubilo, 2015, p. 54), increasing current “signs and symptoms as well as the possibility of triggering new features, for example bone pains” (Giannubilo, 2015, p. 54). Conversely, Gaucher disease is a treatable disorder. With proper enzyme replacement treatment strategies in place, the patient can have an extremely productive life, both socially and economically.

Thus, if both the mother and the father do not have a severe mutation to Gaucher disease, one can even wait until the baby is born before genotyping takes place.

As previously mentioned, in the current scenario, the mother has Gaucher disease and the father is a carrier. Thus, the baby has a 50% chance of being diagnosed with Gaucher disease. With regards to abortion, severe genetic abnormalities pose limited ethical difficulties. Though additional challenging concerns may ensue when the course of the disease is erratic or “unpredictable” and “when the disease is moderate” (Gross, 2002). “While the severity of type 1 Gaucher disease varies substantially and treatment is available, some prospective parents remain cautious about carrying a genetically affected fetus to term” (Gross, 2002, p. 152). While the test for genetic screening of Gaucher disease is simple, accurate and sensitive, it does not predict disease prognosis or severity of clinical manifestations.

In *After Virtue*, Alasdair MacIntyre is of the notion that “both predictability and unpredictability are crucial aspects of human life” (MacIntyre, 1984, p. 104). He held that “for a degree of social structure and regularity” it is essential “to engage in the long-term projects and planning which make life meaningful, while a degree of unpredictability is required for us to be in possession of ourselves and not merely to be the creations of other people’s projects” (MacIntyre, 1984, p. 104).

I contend that maybe we should not only be fascinated with the notion of predictability or non-predictability (genetic testing) of the future *traits* of a person (e.g. a person’s propensity to have Gaucher disease), but rather regard the person holistically with regards to *potential* and look at their future traits pertaining to possible societal and economic benefits as a human being in entirety. Many Gaucher patients have the potential to be highly functional individuals particularly if they are diagnosed early and have adequate access to enzyme replacement therapy are treated timeously and thus have the capacity to live quite happy and fulfilled lives whilst making major economic and societal contributions (Masek, 1999, p. 263) (Weinreb N. , 2002, p. 112) (Hayes, 1998, p. 521).

Should a mother decide to abort her fetus earlier than the third trimester, her decisions could be guided by using wisdom, exercising good judgement and acting with care and thought for the future. However, maternal discretion to abort during the further progression or later on in the pregnancy is normally insufficient both morally as well as ethically to provide sufficient justification. Fetal interest should also be taken into consideration. The expectation of delivering an infant with a chronic, incapacitating and devastating genetic disease generally supplies adequate reason for abortion, however, the contexts unique to Gaucher disease could overturn any forthright conclusions (Gross, 2002).

According to Gross et al, when the disease is treatable, fetal best interests may actually mitigate against abortion. Therefore, the notion of abortion of fetuses “afflicted with Gaucher disease or any similar genetic illness” may present more challenges than initially anticipated (Gross, 2002, p. 159).

A utilitarian approach generally underscores justification for selective abortion. As previously discussed, from a moral perspective, utilitarianism considers the reasonable “consequences which may arise from a particular action” (Graham, 2004). Should a mother decide to terminate a pregnancy due to concerns regarding carrying a fetus with an impairment to term, such a decision would be influenced by the utilitarian approach to moral reasoning.

Lea et al mention the example of a baby born with impairment with the prospects of a “less than optimal life” that would possibly “create a great burden to the parents and society” alike (Lea, 2005, p. 234). In this instance, according to utilitarian principles, it might be better if the baby dies. In reality, ethical circumstances often deal with conflicting values. Although the appropriate action may not always seem well-defined, the direction the medical action must take is evident. There is no strong differentiator between “right” and “wrong” when looking at ethical dilemmas. Both the values and wishes of everyone involved should be taken into account when choosing the best possible outcome. When analyzing this situation, careful thought and consideration of all the influencing factors must be considered. Davis et al argue that utilitarianism is in stark contrast with medical ethics. Davis quotes the example that most hospitals have “a renal dialysis unit for kidney transplants” which could potentially have devastating consequences for healthcare services (Davis, 1997, p. 57).

Davis therefore holds that the *principle of justice* be added to the “principle of utility” when making “ethical decisions about how widely the good” should “be distributed throughout society” (Davis, 1997, p. 57). Also, subscribing to utilitarianism, this may indicate that even though the “greatest number” of people is happy, this could be to the detriment of “the minority” (Davis, 1997, p. 57).

Reflection for selective abortion and hence determining morality of this practice from a utilitarian perspective, commonly make reference to the following individual’s welfare and interests, the fetus (who may be a future individual), the possible next child who may not be conceived due to the parents pre-conceived conception of disease repetition. Lastly society, particularly with reference to the extra financial resources needed to look after and treat a child afflicted with a disability or a hereditary genetic disease (Kushe, 1985, p. 155).

Due to financial pressures, other family’s needs and other circumstances justifying the hedonistic calculus, a utilitarian may question whether an abortion may bring about more happiness for the greatest number of people. Utilitarianism thus mostly pivots around indirect consequences to a greater number of people and not on the positive or negative effects of the proposed act which is ultimately directly related to the individual who will in this instance be directly affected by the act. When considering utilitarianism, it is absolutely impossible to rely on general outright recommendations, since every single case consists of its own pertinent relevant features and therefore should be evaluated on an individual basis, taking into consideration numerous factors. A more important principal to consider in this context which will be described in the next section would be *autonomy*.

### **3.2 Abortion on medical grounds and autonomy**

Generally, the scientific community and society as a whole might not be averse to defend a women’s right to decide to abort a fetus with debilitating genetic defects. *Autonomy* of the mother is regarded as an imperative principle of bioethics. “Immanuel Kant” held that a person has free will and choice and is thus responsible for his/her own actions, acting in accordance with one’s true self, i.e., one’s rational will (Morgan, 2001, pp. 87, 88).

The “duty to respect others’ *autonomy*” reigns supreme “in virtually all ethical situations” (Lea, 2005, p. 235). The word “autonomy” is derived from Greek word “autonomos”, meaning “self-rule” which renders this principle to apply to the rights and interests of individuals (Hewson, 2001, p. ii10) (Beauchamp, 2014, p. 23).

According to Lea et al, autonomy dictates that decisions should be voluntary and “free from coercion” (Lea, 2005, p. 235). According to Petchesky et al, one of the foremost creeds of feminist belief is “that women have a fundamental right to” autonomy and “bodily integrity” (Petchesky, 1986). This unequivocally encompasses “the right to terminate an unwanted pregnancy” (Petchesky, 1986). “The Liberal Theory of Abortion” emphasises the “freedom of choice”, as well as “the right of a woman to make decisions that affect her body” (Beauchamp, 2014, p. 240).

Denbow holds that for pregnant women, respecting autonomy does not always mean capitalizing on a range of options. There are numerous factors that need to be considered to show consideration for a woman’s reproductive independence of choice and self-determination, for instance: societal stigmas, resources available, welfare laws and healthcare systems (Denbow, 2013, p. 228). Should the option of abortion not be available in the instance of high-cost disease, the uncertain future might place almost insurmountable financial and emotional burdens that may in turn put the mother at a significant social and economic disadvantage. Thus, being an autonomous being, should the mother after careful consideration and consultation decide to abort the baby in this instance? I believe that it would not be morally wrong for the mother to abort the cells that are currently called “fetus”.

South Africa has legalized abortion and in terms of the “Choice of Termination of Pregnancy Act (Act 92 of 1996)” (GovernmentGazette, 2008), the mother, being 12 weeks pregnant at this stage, is totally within her legal and ethically autonomous rights to request an abortion at less than 13 weeks without describing in any particular detail what the motives were behind her decision.

If the mother decides to abort, she will never know whether the baby she aborted indeed would have acquired Gaucher disease. Throughout history, the fundamental world view underlying science has been Newtonian. Epistemologically, Newtonian science holds the promise of comprehensive, objective, clear and assured knowledge of past and future.

Conversely, this bygone notion disregards any alternative idea, depicting value, ethics, or creative processes, applying a designation of almost an intricate “clockwork mechanism” to the universe (Heylighen, 2007). However, recently, various scientific developments have contested this one-dimensional picture, pointing towards a much more complex scenario. Cilliers and Heylighen hold that our scientific knowledge of the world is fundamentally *uncertain, complex and unpredictable* (Cilliers, 1998) (Heylighen, 2007, p. 131). Thus, sometimes we have to cope with uncertainty when dealing with the most profound and important issues in life, and although we find ourselves in unknown territory or spaces of moral exception, analytical complexity should be embraced.

Houle holds that abortion debates have stagnated because in her opinion, ethicists tend to work with caricatures of multifaceted phenomena, relying on rules of reason to represent positions that cannot be articulated or explained in logical arguments thereby revealing the utmost complexity of the moral character of abortion (Houle, 2013). According to Houle, we should also consider “spaces of exception” (Houle, 2013). At that stage, the mother will most certainly do the best with the facts that she has access to. Thus, we might never have a clear answer or conclusion in this ongoing debate.

Some contend that abortion is never acceptable and therefore religious and cultural beliefs and stigma of the community should be considered, as well as the expected influence/damage to the family as a whole. This is commonly called the Conservative Theory of Abortion and often a common belief amongst Roman Catholics, but they are by no means its only advocates (Beauchamp, 2014, p. 240). Obviously, the deliberation will include the mother’s degree of autonomy and the rights of the fetus itself. Consideration should be given to provide information and guidance in a non-paternalistic and sensitive manner, anticipating that the mother will find her own answers, confident that she has ultimately made the right choice.

One of the important notions of contemporary utilitarianism and pertinent to the bioethical argument of abortion particular to the fetus, is the concept of personhood (Singer, 1993). According to Tooley et al, “a person is a being who is self-aware” and has the capacity to understand that there is an opportunity or possibility of “continuing the self” (Tooley, 1972, p. 40).

Locke defined a person as a being capable of reflection, aware of being in different times and places and thus, due to awareness, could potentially be deprived of a continued existence (Kushe, 1985, p. 132).

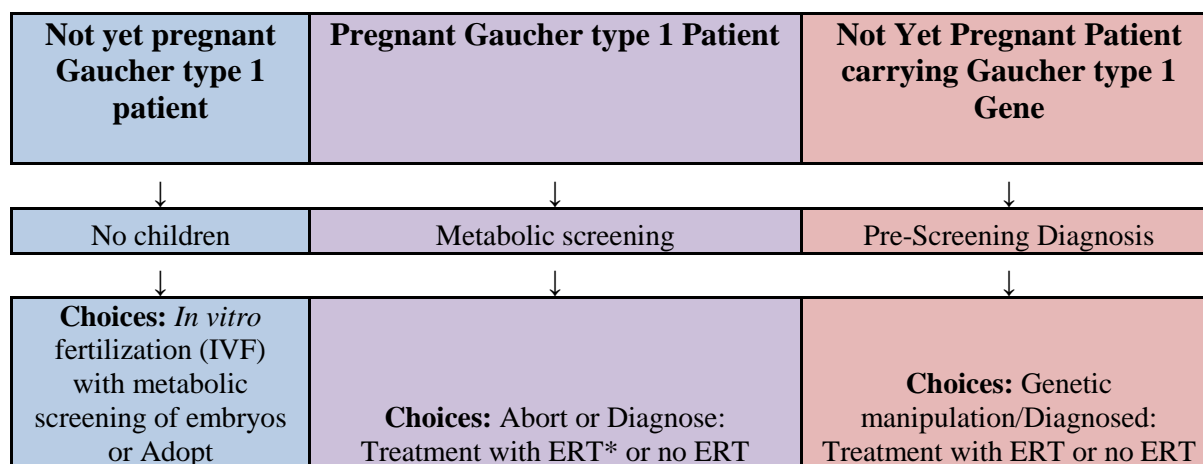
Human life is always considered precious. Baganini et al held that “life is intrinsically valuable in and of itself” and that “existence usually sustains a conscious personal life” with “life projects, personal values and metaphysical beliefs” (Baganini, 2012, p. 91). However, although no one contests that a fetus is alive and that it has numerous possibilities and ambitions left unfulfilled, I agree with Baganini that “it gradually acquires the characteristics that give it such value” (Baganini, 2012, p. 94).

Finally, tremendous financial strain ascribed to the high costs of medical care, mostly long-term, could be accrued from raising a child with especially bone impairments due to Gaucher disease. This may exhaust the family’s resources, compromising the family as a whole. Thus, should the mother, decide to keep the baby and he/she is diagnosed with Gaucher disease, early treatment initiation is imperative to avert debilitating adverse effects of the disease (Masek, 1999, p. 263) (Weinreb N. , 2002, p. 112) (Hayes, 1998, p. 521). In this way, with both baby and mother treated, both can function optimally and contribute successfully to society and hence can become important economic and social contributors (Masek, 1999, p. 264).

Accepting a lack of answers is always extremely difficult because surely there has to be a way to handle ethical dilemmas like this. In order to handle such a dilemma, one should try to consider weighing up all moral principles one by one and apply which is most applicable to the current case and individuals in question. The solution might involve careful consideration and reflection. The final choice lies with the particular individuals and their families in question and if given proper attention to what really matters, and is of value to them, with proper responsibility the essence of what morality really is, might get to a deserving and worthwhile conclusion.

Increasingly apparent from the previous section (as discussed in the Case Study) is that the mother, (Mrs. X), just recently diagnosed with Gaucher Type 1 (a rare disease), will be faced with a life-threatening disease with implications for the fetus and will need to make some ethical choices on behalf of herself and the fetus (See figure 3.2 below on next page).



**Figure 3.2: Possible choices of a female patient with Gaucher type 1:**

\*ERT: *Enzyme replacement therapy*

These ethical choices are not unique, and are typically associated with numerous other genetically inherited rare diseases. My intention with this particular thesis, however, is to concentrate predominantly on the following four ethical issues relating to Gaucher disease, namely genetic screening/testing, disclosure of genetic information, abortion as well as resource allocation.

In conclusion, in addition to uncertainties and complexities associated with some contemporary ethical dilemmas like genetics and selective abortion, there can be no doubt that we currently live in the golden age which opens up a Pandora's Box of possibilities, offering a plethora of opportunities for genetic testing, and hence diagnosis and therapy of rare and chronic genetic disorders such as Gaucher disease. By placing within human power the ability to possibly "foresee" future consequences as well as to have the opportunity of changing the outlook of a disease, previously regarded as given and unchangeable (in our destiny), compels us to reconsider traditional boundaries between injustice and the hand we are dealt. However, this also brings about a range of moral and ethical dilemmas, demanding careful consideration and reflection. I hold that we should maybe use this opportunity of a deepened understanding of genetic issues to contribute to an appreciation of the wealth of human diversity and the vast untapped potential inherent in each of us.

# Chapter 3

## Recommendations

Limited awareness of rare diseases amongst a wider scope of healthcare professionals, as well as limited numbers of geneticists and genetic counsellors are only some of the challenges patients with rare diseases are currently facing in South Africa. As previously discussed, the limited prevalence precludes prioritization of rare diseases for national health programs. Hence, innovative approaches are needed to increase current awareness and to broaden the current scope of knowledge expertise.

We can certainly learn a lot from the European Commission of Public Health's combined efforts to develop "European Centres of Excellence" and "European Reference Networks for rare diseases" (ECPH, 2014). It would be difficult to compete with this sphere of healthcare "where collaboration between 27 different national approaches" is well-organised, and highly resourceful (Baldovino, 2016, p. 359). This European Union task force endeavours to: render "rare diseases more visible by developing proper identification and coding to increase diagnosis", encouraging EU "member states to develop national rare diseases" health policy initiatives to "ensure equal access to prevention, diagnosis, treatment and rehabilitation" and "providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared" throughout Europe "in specific areas" including "research, centres of expertise, access to information, orphan medicines, and screening" (ECPH, 2014).

In the light of all the previous gathered data, my take on the matter is that one could for instance implement some of the following ideas:

### 3.1 Patient treatment access

- Since Gaucher disease, is a chronic disease, the patient will be on enzyme replacement therapy lifelong. Thus, sometimes, the only chance to enter or enrol in a treatment program is when a patient deteriorates. I thus propose a rare diseases treatment waiting list, similar to waiting lists for organ transplants (taking into account medical criteria dependent on prognosis/survival rate, co-morbidities, age/life-expectancy) (Bloom, 1987). A proposal is that an advisory board consisting of treating physicians and other important stakeholders could be formed who will adjudicate which patients might be eligible based on urgency of treatment, clinical signs and symptoms as well as how life-threatening the patient's disease is.
- Thoughts might even be given to a "Rare Diseases National Lottery" which might give all patients with a rare disease an equal opportunity to participate (Brock, 2006, p. 264).

### 3.2 Disease advocates

- More resources should be made available for rare diseases patient support groups like Gaucher Society South Africa ([www.gaucherssa.co.za](http://www.gaucherssa.co.za)) and "Rare Diseases South Africa" (<http://www.rarediseases.co.za>). Patient support groups form an extensive network where patients and relatives with rare genetic diseases can safely associate, communicate and impart and share critical experiences, whilst discovering useful and valuable information and resources. There is a minority voice behind rare diseases in South Africa, which is not strong enough, and it is precisely therefore that this debate needs to take place.

### 3.3 Research

- Lack of research related to rare diseases seems to be a global problem, since recent results from the Rare Diseases Organisation in the UK (RDUK) reveals dissatisfaction with present "funding support given to research into rare diseases" ([www.rarediseases.org.uk](http://www.rarediseases.org.uk)) (RDUK, 2013).

Thus, I suggest increased or ‘ring fenced’ funding for more research into rare diseases. In South Africa, there is a need for more rare disease registries. This will assist with recording the number of affected patients, monitoring the amount and severity of symptoms as well as documenting the natural history of the disease. Moreover, these initiatives will also enhance the visibility to Gaucher disease patients and elucidate their daily needs and problems. This may ultimately accelerate research and development of novel rare disease treatments and enhance drug access and reimbursement through medical aids in South Africa.

### **3.4 Funding**

- I propose that a pool of money from the annual National Health Budget in South Africa be allocated specifically to help patients with rare diseases in South Africa (Brock, 2006, p. 264). This budget should increase yearly. There are many examples of health funding globally. In certain countries, some clinical conditions already have centralized funding structures in place. In France, certain high-cost medicine is accessible via specific centres “who receive funding support” (Hughes D. , 2005, p. 834). The Netherlands are very proactive in the sense that costly “licensed orphan drugs” are added to a list which permits prescription by academic hospitals. Ninety-five percent of these costs are reimbursed by Ministry of Health and 5% from hospital budget (Hughes D. , 2005, p. 834). A pertinent example of resource allocation to Gaucher disease is the newly created Health Fund of Macedonia which since the end of 2016 treats patients with Gaucher disease (Gucev, 2015, p. 151).

### **3.5 Education**

- Training more healthcare professionals to identify and diagnose rare diseases is an important initiative that needs more attention. Multidisciplinary academic rare disease workshops may be held including various disease specialities, amongst others, geneticists, paediatricians, physicians, haematologists, endocrinologists and surgeons.

The aim would also be to ultimately create specialised disease centres which in itself would generate more publicity. Also, perhaps more emphasis should be placed to include rare diseases in curriculums of certain disease specialities to enhance earlier diagnosis and to create a larger pool of rare disease experts.

- There is also a need for augmented online Continuing Medical Education (CME) platforms, focusing exclusively on rare diseases. In addition, novel technologies, such as telemedicine or web based platforms that increase interconnectivity between rare disease experts and patients globally may be considered.

### **3.6 Publicity**

- The publicity behind AIDS and tuberculosis is extremely high. However, rare diseases receive far less publicity (Kling, 2013, p. 95). Publicity for rare diseases can be increased through the platforms of various rare diseases societies and with funding from other stakeholders with vested interests. Herewith a few pertinent examples:
  - Increased public rare disease awareness may be created by launching campaigns including posters and patient information leaflets in doctor's waiting rooms and at well-attended popular public events as well as by inviting rare disease experts to host expert talks on radio stations.
  - Improved awareness can also be created by travelling rare disease ambassadors, not only in South Africa, but also globally, to share their stories with yet undiagnosed family members or newly diagnosed patients.

Obviously, the above examples would need to comply with the current guidelines of the Marketing Code of Practice which was published in February 2015 ([www.marketingcode.co.za](http://www.marketingcode.co.za)).

### **3.7 Final recommendations:**

My conclusion, with regards to this case study in particular, is that since untreated female patients with Gaucher disease are at a significant risk of recurrent fetal loss, I would, after careful consultation and informed consent, recommend treatment for the pregnant lady involved. In this instance the pregnant patient after comprehensive and careful consultation did reveal her diagnosis to her spouse, who was subsequently also tested. His test results showed him to be a carrier of Gaucher disease. Because the needs of families with individuals with rare diseases cannot be emphasised enough, I would also recommend psychological care in addition to sufficient information to make informed decisions. Reality-orientated counselling should take place at all stages of the process with a physician well versed in the pathophysiology and treatment of Gaucher Type 1 disease. The patients' best interests should always be top of mind. The cost to a family of watching a child suffer for years before dying is incalculable.

Thus, with regards to allocation of treatment for rare diseases and in particular type 1 Gaucher disease, more efforts should be made towards access to enzyme replacement therapy for most, if not all patients through innovative initiatives. Reimbursement of treatment of rare diseases invariably creates immeasurable conflicts between the claims of society versus individuals. My view is that while the numerous ethical theories and reflection may not provide a clear answer to every possible ethical dilemma, they may, however, afford the necessary elucidation in terms of context and structure.

Each and every ethical theory gives a different perspective or brings some valid point to the fore, giving us diverse views and means and moral applications. None is perfect. And will never be. We are all, after all, only human. If, however, we endeavor to do the best in the circumstances with the most facts in hand, we cannot stray too far from the moral path. We need to try to incorporate the most sound and most suitable solution according to our best intentions whilst being true to others and ourselves.

Ethics is complex and can in no manner, whatsoever, be adequately addressed by any set of imperfect rules, formulas or precise theories. Every single case we will ever be dealing with is different. Therefore, ethics require from us unprejudiced, open-minded consideration of

each individual patient's interests. A suggestion would be even closer scrutiny of costs associated with rare diseases to assist funders to ascertain proportion of resources needed to accommodate rare diseases within the healthcare realm versus other more commonly encountered diseases. It is my view that it is important to make some cost comparisons between low prevalence rare diseases with other high prevalence disorders receiving larger allocations in South Africa's National Health Budget. Maybe a revised framework with greater inclusion for rare diseases like the ethical framework previously alluded to and proposed by Pinxten et al is required for decision making and distribution of healthcare resources (Pinxten, 2012, p. 148).

Finally, many ethical dilemmas can be extremely acute and complex with no universal practices that can settle these issues. Every patient has an explicit and inherent right to life, opportunity and realization of potential but this can be in conflict with justice in the scenario of limited resources.

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