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Access to healthcare in the age of CRISPR: An analysis of the right to heritable human genome editing in the context of the Tuberculosis epidemic in South Africa

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DECLARATION

I, Tamanda Kamwendo, hereby declare that except where specified otherwise this project is an original piece of work by me which is made available for photocopying and for inter-library loan.

Signed: _____  _____

DEDICATION

This thesis is dedicated to the memory of my Father

Professor Gregory H Kamwendo

May his memory forever be a comfort and blessing.

You taught me about dreams and how to catch them!

With love and eternal appreciation! 

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First and foremost, all praises and glory to God for his goodness throughout this journey.

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ABSTRACT

Tuberculosis (TB) is the leading cause of death from infectious diseases in South Africa and a major risk to global health security. Although notable progress has been made towards TB control, its effectiveness has been limited, partly due to acquired resistance during the first-line TB treatment or poor patient adherence to the treatment. Considering that genetic factors play an important role in one's susceptibility to TB, it is imperative that all aspects of vertices of the TB triad — a susceptible host gene, pathogen, and environment — be considered in formulating treatment. CRISPR-CasX is a revolutionary new approach to genetic modification that promises effective disease treatment and control in humans. This thesis explores the right to heritable human genome editing in South Africa in the specific context of TB treatment.

Against this backdrop is the uncertainty of the ambit of the Constitutional commitment to ensure that all South Africans have access to healthcare services such as gene-editing services. As a result, the application of gene-editing technology for TB treatment is contingent on how this the right of access to healthcare services is interpreted. This thesis endeavours to show how the right of access to healthcare should be interpreted as being inclusive of access to gene-editing technology.

This study hence serves as an appraisal for South Africans on how to demand access to gene-editing services as a legal right in the search for a suitable treatment for TB. The thesis also provides momentum for South African policymaking by providing recommendations for research and the clinical use of CRISPR therapeutics as a medicinal product as the country has no gene-editing-specific policies or statutes.

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LIST OF TERMS AND ACRONYMS

DNA – Deoxyribonucleic acid. This is the molecule inside cells that contains the genetic information responsible for the development and function of an organism.

CRISPR– Clustered Regularly-Interspaced Short Palindromic Repeats

CRISPR-CasX – Clustered Regularly-Interspaced Short Palindromic Repeats- associated RNA guided endonuclease CasX

CasX – an RNA-guided DNA endonuclease that generates a staggered double-stranded break in DNA.

Ex vivo – (of a process) performed or taking place outside of the living body.

Gene – This is a basic unit of heredity which is transferred from a parent to offspring

Genome – The genome is the entire set of DNA instructions found in a cell.

Genome editing – the deliberate alteration of a cell's genome through altering DNA.

Germline editing – is the process by which the genome of an individual is edited in such a way that the change is heritable.

In silico – (of scientific experiments or research) conducted by means of computer modelling or simulation.

In vivo – (of a process) performed or taking place inside a living body.

In vitro – (of a process) performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.

MDR-TB – Multidrug-Resistant TB

Monogenic disease – A genetic disease caused by variation in a single gene.

Polygenic disease – A genetic diseases that is caused by the combined action of more than one gene.

RNA – Ribonucleic acid. This is a nucleic acid present in all living cells that has structural similarities to DNA.

Somatic editing– is the process by which the genome of an individual is edited to induce non-heritable changes.

XDR-TB – Extremely drug resistant TB

CHAPTER 1

INTRODUCTION

*'The devil is already at the door, cleverly disguised as [gene editing].' —**Jeremy Rifkin***

I. BACKGROUND OF THE STUDY

Tuberculosis (TB) is an ancient disease yet remains a threat to global health. Although deaths due to TB seem to be decreasing, TB continues to be the leading cause of death in South Africa.[1] Robert Koch, a German doctor, first identified the disease's causal agent in 1882 as the 'tubercle bacillus' which was later named the Mycobacterium tuberculosis (MTb) in 1886.[2] Before the nineteenth century, TB was presumed to be inherited or spontaneous thus eliminating the idea that a coughing patient could spread their consumption to a healthy person. It therefore took decades to demonstrate that TB could be spread from person to person, from person to animal, or from animal to person.[3] Koch was then able to demonstrate that the ailment was caused by an external cause, an infectious bacterium, — the Mycobacterium tuberculosis. His studies also showed that the bacterium was transmitted from person to person only through contact with an infected person or animal, all of which marked the start of a journey to the disease's discovery and eventual drug discovery.[4]

Furthermore, with increasing global migration, TB was acknowledged as a global health-security problem, rather than a purely health-related problem. The WHO defines global public health security as

> 'activities required, both proactive and reactive, to minimize the danger and impact of acute public health events that endanger people's health across geographical regions and international boundaries.'[5]

[1] GJ Churchyard, LD Mametja & L Mvusi, 'Tuberculosis Control in South Africa: Successes, Challenges and Recommendations' (2014) 104(3) *South African Medical Journal* 244.
[2] E Cambau and M Drancourt, 'Steps towards the Discovery of Mycobacterium Tuberculosis by Robert Koch, 1882' (2014) 20(3) Clinical Microbiology and Infection 196, 196.
[3] ibid 197.
[4] R Koch, 'Die Äetiologie Der Tuberkulose' (1882) 15 *Berliner klinische Wochenschrift* 222.
[5] World Health Organization, 'Health Security' <https://www.who.int/health-topics/health-security#tab=tab_1> accessed 13 October 2022.

The goal of health security in today's global public health may be regarded as to safeguard cross border populations from health threats. It stems further from the ordinary epidemiologic methodologies for emolliating public health issues.[6] Generally, human security is said to comprise of seven dimensions —food, economic, health, personal, political, environmental and community — all aimed at protecting the essence of human life against serious threats that are inconsistent with long-term human fulfilment.[7] Epidemics such as TB are considered to be threats to human security and this brought about political attention to the fight against TB which has led to TB issues finding their place in International documents dealing with global security. Accordingly, Goal 3.3 of the Sustainable Development Goals (SDGs), lists the TB epidemic as one of the major health challenges to be resolved by 2030. 2016 also marked the birth of the WHO (World Health Organization) End TB Strategy. This 20-year strategy aims to end the global TB epidemic by 2035. Its main targets are to reduce TB deaths by 95 per cent and new infections by 90 per cent.[8] It also aims to ensure that no family is burdened with catastrophic expenses due to TB.

In 2019, 1.4 million individuals died from TB worldwide, with an estimated 10.0 million developing active TB illness.[9] In bringing the problem home, in 2019, TBFacts.org reported that 360 000 people in South Africa contracted TB and 58 000 of them died as a result of TB.[10] There was however a twenty per cent decrease in new TB incidences between 2015 and 2020 making South Africa one of the six nations to reach the 2020 End TB Strategy milestones.[11] However, due to the COVID-19 pandemic, TB health services have been disrupted globally, which has not only increased the number of TB cases and TB-related fatalities, but also stalled efforts to reach the long-term objective of ending TB.[12] This is so because COVID-19 may

[6] William Aldis, 'Health Security as a Public Health Concept: A Critical Analysis' (2008) 23(6) *Health Policy and Planning* 369, 371–33.
[7] Ranja Rokvic & Jeftic Zoran, 'Health Issues as Security Issues' (2015) 67(6) *Vojno Delo* 53, 53.
[8] Haruka Sakamoto, Lee Sangnim, Aya Ishizuka et al, 'Challenges and Opportunities for Eliminating Tuberculosis – Leveraging Political Momentum of the UN High-Level Meeting on Tuberculosis' (2019) 19 *BMC Public Health* 77.
[9] Jeremiah Chakaya, Mishal Khan & Francine Ntoumi, 'Global Tuberculosis Report 2020 – Reflections on the Global TB Burden, Treatment and Prevention Efforts' (2021) 113(1) *International Journal of Infectious Diseases* 7, 7.
[10] 'Turning the Tide on TB' *National Institutes for Communicable Diseases* (7 March 2022) <https://www nicd.ac.za/turning-the-tide-on-tb/> accessed 1 August 2022.
[11] ibid. The TB incidence rate is defined as the proportion of new TB cases in a population over a specific period.[11]
[12] 'Stop TB Partnership. Civil Society-Led TB/COVID-19 Working Group. The Impact of COVID-19 on the TB Epidemic: A Community Perspective. Geneva, Switzerland: Stop TB Partnership, 2020.' <http://www.stoptb.org/assets/documents/ r e s o u r c e s/p ubli c a tion s/ a c sm/Ci vil%2 0 S ocie t y%2 0 Report%20on%20TB%20and%20COVID.pdf?fbclid¼ IwAR3SOY4kyBs5a_35HIeUhcvwRIWspePA4vVHESqc Qxio7G4irivJ90cSU8k> accessed 13 November 2021.

have impeded the treatment of TB patients due to inadequate treatment support and drug stockouts. Such a disturbance raised the possibility of treatment delays as well as lower treatment adherence, both of which are likely to affect the outcomes of TB treatment. Regrettably, a decade of progress in emolliating the TB epidemic has been undone by the COVID-19 pandemic. This has been evidenced by a rise in TB deaths globally in 2020 for the first time since 2012.[13]

The WHO predicts that at least 500,000 additional people may have passed away from TB in 2020 alone yet not recorded as such.[14] More so, further projections show that over the next five years, TB incidences, and particularly TB mortality globally, would rise by about five to fifteen per cent, leading to tens of thousands more TB fatalities.[15] Although these evaluations have been predicated on a number of assumptions that, ideally, should be assessed in light of empirical data, actual data also reveals that due to a lack of access to TB diagnosis and treatment in 2020, the number of TB-related deaths in South Africa had returned to the levels seen in 2017.[16] More so, it has been reported that, in South Africa, the COVID-19 epidemic has slowed down TB testing, diagnosis, and therapy, with treatment success rates dropping from 80 per cent to 76 per cent in September 2021.[17] Since the global village is still experiencing health related accessibility challenges as a result of the COVID-19 pandemic, it is not a farfetched hypothesis that the projections made for the next five years might prove to be true.

Tracking national budgetary allocations is also critical to understanding the extent of the TB epidemic on South Africa's healthcare system. Budget allocations to the Department of Health for HIV and TB have grown by seven per cent annually, that is, from R11.0 billion in 2013/14 to R18.3 billion in 2017/18.[18] Astoundingly, in the 2022/23 financial year, R55 billion — 86 per cent of total allocation — was allocated to health service activities related to HIV and TB.[19] Despite the country's fiscal constraints, TB budgetary allocations are anticipated to

[13] Eskild Petersen and others, 'World TB Day 2022: Revamping and Reshaping Global TB Control Programs by Advancing Lessons Learnt from the COVID-19 Pandemic' [2022] *International Journal of Infectious Diseases*.
[14] CF McQuaid, A Vassall & T Cohen, 'The Impact of COVID-19 on TB: A Review of the Data' (2021) 25(6) *The International Journal of Tuberculosis and Lung Disease* 436, 436.
[15] ibid.
[16] 'Turning the Tide on TB' op cit note 10.
[17] See, Health Department Budget Vote 2022/23, available at https://www.gov.za/speeches/minister-joe-phaahla-health-dept-budget-vote-202223-10-may-2022-0000. Accessed 10 August 2022
[18] Nhlanhla Ndlovu and others, 'A Review of Health, HIV and TB Resource Allocation and Utilisation in South Africa 2013/14 - 2020/21' [2019] *South African Health Review*.
[19] See https://www.parliament.gov.za/news/minister-health-concerned-about-decrease-health-budget-medium-term. Accessed 12 September 2022.

increase in the future. This will be amplified by the growing rate of new TB infections that continue to put pressure on the government's overall response to the TB epidemic.

II. SITUATION ANALYSIS OF DRUG RESISTANT TUBERCULOSIS IN SOUTH AFRICA

It is indisputable that mandatory childhood vaccinations have emolliated a number of epidemics from the past such as Polio and smallpox. However, there are several hurdles in fighting TB infections and achieving the intended herd immunity through normal vaccination. BCG (Bacillus Calmette-Guerin) is the first and only available TB vaccine.[20] In South Africa, all children are given the BCG vaccine at birth which assists babies to develop antibodies against TB. However, BCG has proven not to be effective against pulmonary TB and is only thirty per cent effective in preventing active TB.[21] Studies also show that its protective efficacy is limited to infants and wanes as an individual approaches teenage hood.[22] Additionally, the use of BCG has been linked to adverse outcomes in HIV-positive infants and those with severe immunodeficiencies. These individuals may develop disseminated BCG infection and other complications because of vaccination, which poses a serious risk to patients living in areas with a high prevalence of HIV-TB disease such as South Africa.[23] Although there are currently at least sixteen vaccine candidates in active clinical trials, the race to develop a more effective TB vaccine is a slow and lengthy project. As such, one other possibility being explored is whether the efficacy of the current BCG vaccine itself should simply be improved.[24]

Currently, a phased multidrug combination is recommended for treating TB, starting with a two-month intense phase of rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB).[25] Then, any bacilli that may have not been eliminated are treated with RIF and INH during a protracted continuation phase. It is important to note that these drugs are

[20] Amy Green, 'IN-DEPTH: The Slow-Motion Race for a TB Vaccine' *Spotlight* (19 October 2020) <https://www.spotlightnsp.co.za/2020/10/19/in-depth-the-slow-motion-race-for-a-tb-vaccine/> accessed 8 April 2020.

[21] 'Tuberculosis in South Africa' *Wits University Donald Gordon Medical Centre* <http://www.dgmc.co.za/tuberculosis-in-south-africa> accessed 8 April 2021.

[22] Punam Mangtani, Ibrahim Abubakar and Cono Ariti, 'Protection by BCG Vaccine against Tuberculosis: A Systematic Review of Randomized Controlled Trials' (2014) 58(4) *Clinical Infectious Diseases* 470, 471.

[23] Anneke C Hesseling, Ben Marais and Robert Peter Gie, 'The Risk of Disseminated Bacille Calmette-Guerin (BCG) Disease in HIV-Infected Children' (2007) 25(1) *Vaccine* 14, 15.

[24] Green op cit note 20.

[25] Fabio Luciani, Scott A Sisson & Honglin Jiang, 'The Epidemiological Fitness Cost of Drug Resistance in Mycobacterium Tuberculosis' (2009) 106(34) *Proceedings of the National Academy of Sciences of the United States of America* 14711, 14711.

administered to patients who are deemed 'new patients' and who have never received anti-TB treatment before or those who have received treatment for less than one month.[26]

However, South Africa is heavily challenged with Multidrug-Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB). It has the second-largest number of diagnosed MDR-TB cases after India.[27] Drug resistant TB occurs when TB patients are resistant to the most effective first-line TB drugs — rifampicin and isoniazid. A person is considered to be a DR-TB patient once it is determined that they are rifampicin resistant and GeneXpert positive.[28] Keeping in mind that DR-TB is only diagnosed by testing, a child who exhibits TB symptoms and has been in close contact with a DR-TB patient is the sole exception to this rule. As a result of their incapacity to expectorate and the paucibacillary nature of childhood TB, diagnosing DR-TB in children is typically challenging. Accordingly, due to the limited availability of this data, it is believed that the proportion of DR-TB in children is comparable to that of adults given that the primary cause of TB in children is primary transmission from adults.[29]

Treatment for MDR-TB requires the use of second-line drugs, which are often more toxic than first-line medications. The WHO currently defines three groups of drugs used to treat drug-resistant TB. Group A which is the first line of drugs contains Bedaquiline, Levofloxacin and Linezolid. These drugs are associated with an increase of cardiac arrhythmia and bone marrow suppression.[30] If a patient shows resistance to these drugs, Group B drugs — Terizidone and Clofazimine are introduced. Adverse effects on these drugs include neuropsychiatric side effects and peripheral neuropathy. Group C drugs are mostly used in when Group A or B drugs are not tolerated. Group C drugs are commonly referred to as the toxic drugs and include Delamanid, Pyrazinamide, Ethambutol and high-dose INH (hINH).[31]

[26] ibid 14712.
[27] Helen Cox, Lindy Dickson-Hall, Waasila Jassat et al, 'Drug-Resistant Tuberculosis in South Africa: History, Progress and Opportunities for Achieving Universal Access to Diagnosis and Effective Treatment' (2017) 1 *South African Health Review* 157.
[28] M Muller, 'An Overview of the New Rifampicin-Resistant Tuberculosis Regimens Available at Decentralised Drug-Resistant Tuberculosis Sites for Persons Older than Six Years' (2020) 62(1) *South African Family Practice*.
[29] Nomonde Ritta Mvelase and others, 'Evolving Rifampicin and Isoniazid Mono-Resistance in a High Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Region: A Retrospective Data Analysis' (2019) 9(11) *BMJ Open* 5.
[30] Muller op cit note 28.
[31] ibid.

Treatment for DR-TB may last up to two years and involves a daily intramuscular injection for the first four to eight months.[32] More so, treatment results for DR-TB in South Africa are very poor. In 2013, South Africa's average MDR-TB treatment success rate was 47.2 per cent. According to a study conducted in 2015 to test rifampicin resistance, KwaZulu-Natal was listed as the MDR-TB hotspot with seven of the eleven provincial districts reporting above the national average ratios of rifampicin resistance.[33] Furthermore, according to the 2018 report, only 55 per cent of MDR/RR-TB patients received treatment success, which indicates that although treatment outcomes may be improving, they are still dismal.[34]

Over time, TB treatment constraints have also altered the nature of TB disease itself resulting in drug-sensitive strains becoming chronic and lethal by creating resistance to current antibiotics.[35] While the widespread opinion was that TB drug resistance is mainly due to acquired resistance during the first-line TB treatment or bad patient adherence to the treatment, studies have shown that there is high transmission of DR-TB strains in South Africa and 55 per cent of these XDR-TB patients had never received prior TB treatment, illustrating direct transmission.[36] One often-forgotten effect of TB is the enormous financial strain it puts on patients and their families. In addition to treatment expenditures, TB patients are compelled to take time off work, putting them at danger of becoming impoverished. As a result, studies have shown that due to financial reasons, most patients stop their TB treatment before six months leading to re-infections and incidents of MDR-TB.[37]

It is therefore evident that treating TB with monotherapy has, in most instances, proven to be ineffective.[38] Jeremy Rock avers that there is a poor understanding on the physiological mechanisms that limit the efficacy of the current forms of TB treatment. He argues that the reasons for reduced efficiency could be either bacteria-centric or drug-centric.[39] The mycobacteria are believed to exist in diverse physiologic states within the infected host, which may render it resistant to one or more antibiotics. Hence, this drug-tolerant mycobacterium can

[32] World Health Organization *Global tuberculosis report 2015*. WHO/HTM/TB/2015.22. Geneva: WHO; 2015. Available from: http://www.who.int/tb/publications/global_report/en/, accessed 26 August 2019.
[33] Deputy President Cyril Ramaphosa. World TB Day, 23 March 2016. Available at https://www.gov.za/speeches/deputy-president-cyril-ramaphosaaddress-mark-world-tb-day-marapong-stadium-lephalale, accessed 28 August 2019.
[34] 'World Health Organization. Global Tuberculosis Report.' (2018) 69 *Pharmacol Rep* 683.
[35] Mike Frick, Ian Henry and Erica Lessem, 'Falling Short of the Rights to Health and Scientific Progress: Inadequate TB Drug Research and Access' (2016) 18(1) *Health and Human Rights Journal* 11.
[36] Cox, Dickson-Hall & Jassat op cit note 27 at 159.
[37] Ibid 80–81.
[38] Jeremy Rock, 'Tuberculosis Drug Discovery in the CRISPR Era' (2019) 15(9) *PLoS Pathogens* 3–5.
[39] Ibid 6.

survive otherwise lethal concentrations of antibiotics. Also, the different medicines access the bacteria residing in distinct pathological lesions with varying efficacy (drug-centric).[40] Cumulatively and notwithstanding other social factors, these factors have contributed to the hard battle against TB. The burden of the TB epidemic as witnessed in South Africa is a compelling reason for alternative treatment options such as human genome editing.

III. TUBERCULOSIS TREATMENT IN THE CRISPR ERA

Not long ago, heritable human genome editing may have been merely a theoretical concept, but clinical applications of CRISPR are rapidly emerging. Particularly, the advent of CRISPR-CasX has revolutionised human genetics as it enables editing of one's DNA with remarkable precision. CRISPR-CasX could be used for treating human disease in three fundamental ways: (1) fighting both viral and bacterial infections, (2) editing somatic cells, and (3) editing germline cells. CRISPR CasX allows targeted genetic material to be added, removed, or altered at particular locations in the genome to treat or prevent both viral and bacterial infections.[41] Human genome editing could therefore be a solution to antibiotic-resistant TB[42] and other inheritable genetic diseases currently straining the country's financial budget.[43]

Following evolving research, CRISPR has allowed genetic modifications in both host cells and the pathogens themselves to emolliate various diseases.[44] Since the debut of CRISPR-Cas9 in 2013, the feasibility of human genome editing has been tested through a series of animal studies.[45] That is, numerous studies have attempted to use this technology to remedy several genetic defects in animal models of human disease.[46] Most of these studies in animal models have been successful in correcting genetic defects thus offering convincing early proof of the potential use of CRISPR to treat and/or prevent TB. More so, the first approval of a CRISPR therapy in 2023 represents a major milestone in setting expectations for more CRISPR

[40] Ibid.
[41] H Bhur & R Jan Lebbink, 'Harnessing CRISPR to Combat Human Viral Infections' (2018) 54 *Immunology* 124.
[42] Harvard University researchers have already used CRISPR-Cas9 to kill antibiotic-resistant tuberculosis. See AK Singh, X Carette and LP Potluri, 'Investigating Essential Gene Function in Mycobacterium Tuberculosis Using an Efficient CRISPR Interference System' (2016) 44(18) *Journal of Nucleic Acids Research* 2–10.
[43] Noah C Chauvin, 'Custom-Edited DNA: Legal Limits on the Patentability of CRISPR-Cas9'S Therapeutic Applications' (2018) 60(1) *William & Mary Law Review* 308.
[44] M Doerflinger and others, 'CRISPR/Cas9—The Ultimate Weapon to Battle Infectious Diseases?' (2017) 19 *Cellular Microbiology* 1.
[45] Rodolphe Barrangou & Andrew P May, 'Unraveling the Potential of CRISPR-Cas9 for Gene Therapy' (2015) 15(3) *Expert Opinion on Biological Therapy* 313.
[46] Ibid.

therapies to come. In 2022, clinical trials for CRISPR based treatments for sickle cell disease were successful bringing the potential of CRISPR based treatment closer to patients.[47]

Using CRISPR-CasX to cure TB is one of the great promises presented by heritable human genome editing. Moreover, studies have proven that TB is not only caused by the bacterium but rather host genes that impact an individual's susceptibility to TB.[48] In one study, 141 people without a history of TB (healthy individuals) and 135 cases of TB had their blood samples collected for DNA extraction. This study examined the association between TB susceptibility and polymorphisms in the *VDR, SLC11A1, and IL10* genes. It was found that the *IL10* gene was strongly correlated with TB susceptibility. Other individuals in the study displayed protection to TB due to high *VDR* gene production and low *IL10* production.[49] Another study conducted on mouse models — which have proven to be a powerful tool in understanding TB susceptibility pathways — revealed that mice that are deficient in producing *Th1* cells or the cytokine interferon gamma (IFN) are highly susceptible to TB infections.[50] These studies demonstrate that the immunological response to TB and the clinical development of TB are greatly influenced by host genetic variables. TB has now been identified as a multifactorial disease with host gene, pathogen, and environmental variables all contributing to active TB disease growth. Consequently, history has proven that it is impossible to deter or cure TB by medical alternatives alone.[51]

Furthermore, studies have shown that black people are twice as likely as white people residing in the same environment to become infected with TB.[52] A study conducted at a nursing home showed that in nursing homes with a single white TB patient, 17.4 per cent of the black residents and 11.7 per cent of the white residents contracted TB whereas in nursing homes with

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[47] See Rock op cit note 38 at 2 and https://www.pharmaceutical-technology.com/features/crispr-gene-therapies-is-2023-a-milestone-year-in-the-making/.

[48] R Bellamy, 'Genetic Susceptibility to Tuberculosis in Human Populations' (1998) *Genetics and Pulmonary Medicine* 592.

[49] CA Silva and others, 'Investigation of Genetic Susceptibility to Mycobacterium Tuberculosis (VDR and IL10 Genes) in a Population with a High Level of Substructure in the Brazilian Amazon Region' (2020) 98 *International Journal of Infectious Diseases* 447, 449.

[50] Clare M Smith and others, 'Host-Pathogen Genetic Interactions Underlie Tuberculosis Susceptibility in Genetically Diverse Mice' [2022] *Genetics and GenomicsMicrobiology and Infectious Disease*.

[51] Prof Eileen Hoal, 'The White Plague Came to Africa: Genetic Susceptibility to Tuberculosis and the Impact of Ancestry'
<https://www.google.com/search?q=THE+WHITE+PLAGUE+CAME+TO+AFRICA%3A+GENETIC+SUSCEPTIBILITY+TO+TUBERCULOSIS+AND+THE+IMPACT+OF+ANCESTRY&rlz=1C1CHBD_enZA844ZA844&oq=THE+WHITE+PLAGUE+CAME+TO+AFRICA%3A+GENETIC+SUSCEPTIBILITY+TO+TUBERCULOSIS+AND+THE+IMPACT+OF+ANCESTRY&aqs=chrome..69i57.2191j0j4&sourceid=chrome&ie=UTF-8#,> accessed 10 September 2019.

[52] WW Stead and others, 'Racial Differences in Susceptibility to Infection by Mycobacterium Tuberculosis' (1990) 322(7) *The New England Journal of Medicine* 422, 422.

a single black patient, 12.4 per cent of the black residents and only 7.7 per cent of the white residents contracted the disease.[53] This demonstrated that black residents of the nursing home were more susceptible to TB as compared to the whites. In 2020, the United Stated of America also recorded that the rate of TB cases among Black/African Americans is eight times higher as compared to white persons.[54] A genome-wide study conducted on Zulus and Cape Coloureds to identify areas in the human genome containing TB-susceptibility genes has also shown that TB susceptibility is not monogenic.[55] More than two regions in the genome showed evidence of TB-susceptibility genes.[56] Recent genetic research has revealed that the KhoeSan communities of Southern Africa are the earliest known indigenous residents of the coastal regions of the south-western Cape and there is a significant KhoeSan genomic contribution to the Cape Coloured population hence their susceptibility to TB.[57] This is also backed by a study which revealed that the Western Cape in South Africa, — notably among the admixed South African Coloured population, — has the second-highest prevalence of TB in the world.[58] Another study conducted on both monozygous and dizygous twins indicated a higher concordance among the monozygous twins. This demonstrates that genetic factors play an important role in one's susceptibility to TB[59] and proposes that the host gene plays an important role in the development of TB. It is only indispensable that host genes should become the new targets for the prevention and treatment of TB.[60]

Conversely, scientists have succeeded in using CRISPR CasX technology to insert the NRAMP1 gene in cows in vitro to make them resilient against bovine TB.[61] Buoyed by its success, gene silencing using CRISPR has also been used on *mycobacteria* as well as a large number of other bacterial species of industrial interest. Gene silencing alters the bacterial

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[53] ibid 422–424.

[54] Centers for Disease Control and Prevention, 'Reported Tuberculosis in the United States, 2020' (2020) <https://www.cdc.gov/tb/statistics/reports/2020/default htm> accessed 13 October 2022.

[55] Monogenic diseases are those that result from modifications in a single gene. See https://www.who.int/genomics/public/geneticdiseases/en/index2 html, accessed 11 September 2019.

[56] R Bellamy, N Beyers and PWJ Keith, 'Genetic Susceptibility to Tuberculosis in Africans: A Genome-Wide Scan' (2000) 97(14) *Proceedings of the National Academy of Sciences of the United States of America* 8007–8009.

[57] Caitlin Uren, 'Investigating Southern African Genetic Diversity and its Role in TB Susceptibility' (PhD thesis (Human Genetics), Stellenbosch University 2017).

[58] Emile Chimusa and others, 'Genome-Wide Association Study of Ancestry-Specific TB Risk in the South African Coloured Population' (2014) 23(3) *Human Molecular Genetics* 796, 796.

[59] Bellamy op cit note 48 at 589.

[60] Li Cai, Zhan Li, Xuhua Guan et al, 'The Research Progress of Host Genes and Tuberculosis Susceptibility' (2019) *Oxidative Medicine and Cellular Longevity* 1.

[61] Scientists have also successfully used CRISPR for targeted gene silencing of Mycobacterium tuberculosis. See https://www.genomeweb.com/gene-silencinggene-editing/crispr-researchers-create-tb-resistant-cattle, accessed 1 July 2019.

metabolic capacity and its resistance to antimicrobial peptides making it less likely to express itself in the human body.[62] More so, CRISPR TB[63] offers an improved diagnostic method which may provide an early, rapid, and accurate TB test due to its highly sensitive nature, ensuring that people are not left undiagnosed but instead receive the necessary treatment timeously. CRISPR-TB was used in finding TB in 80 per cent of children with unconfirmed TB, who had gone undiagnosed using the conventional methods of TB detection such as Xpert and TB culture. This is one of the promises offered by CRISPR in reducing child mortality considering that earlier in the chapter it was discovered that most children particularly those with DR-TB go undetected using sputum-based assays.[64] This demonstrates that non-sputum-based assays such as using CRISPR are also vital in improving TB diagnosis and TB treatment monitoring. The purpose of the next section is to discuss how CRISPR therapies, once set for clinical applications, will reach the masses, as well as its various limitations.

IV. HOW WILL CRISPR BE DELIVERED TO THE MASSES

The main attraction of human genome editing lies in its proposed ability to ameliorate TB with a single procedure.[65] However, the delivery of the CRISPR system for efficient human genome editing is challenging due to the molecular weight of the CasX protein which makes it difficult to penetrate the cell membrane.[66] Furthermore, once inside cells, the CasX protein must survive cell degradation processes and translocate into the nucleus for efficient gene editing.[67]

Accordingly, there are two possible approaches to the current TB disease burden through human genome editing. The first possible way is to make edits in somatic cells — also referred to as gene therapy — for treating TB. However, the downside of somatic editing is that the outcomes of somatic cell edits are limited to the person being treated and will not be transmitted to future generations.[68]

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[62] G Ramachandran & D Bikard, 'Editing the Microbiome the CRISPR Way' (2019) *Philosophical Transactions of the Royal Society of London* 6.
[63] This is an optimised CRISPR-mediated tuberculosis (CRISPR-TB) assay used to detect Mycobacterium tuberculosis cell-free DNA (Mtb-cfDNA) in humans.
[64] Zhen Huang and others, 'CRISPR Detection of Circulating Cell-Free Mycobacterium Tuberculosis DNA in Adults and Children, Including Children with HIV: A Molecular Diagnostics Study' (2022) 3(7) *The Lancet Microbe* e482, e482-490.
[65] Craig A Hodges & Ronald A Conlon, 'Delivering on the Promise of Gene Editing Forcystic Fibrosis' (2019) 6 *Genes & Diseases* 104.
[66] Bon Ham Yip, 'Recent Advances in CRISPR/Cas9 Delivery Strategies' (2020) 10 *Biomolecules* 6.
[67] Ibid.
[68] National Academies of Sciences, *Human Genome Editing: Science, Ethics, and Governance* (National Academies Press 2017).

Alternatively, germline gene editing could be pursued. Germline gene editing affects all cells in the human body — including eggs and sperms — and is therefore the edits are passed on to future generations,[69] thereby serving as immunisation for his/her progenies. The figure below illustrates the difference between somatic and germline gene editing.

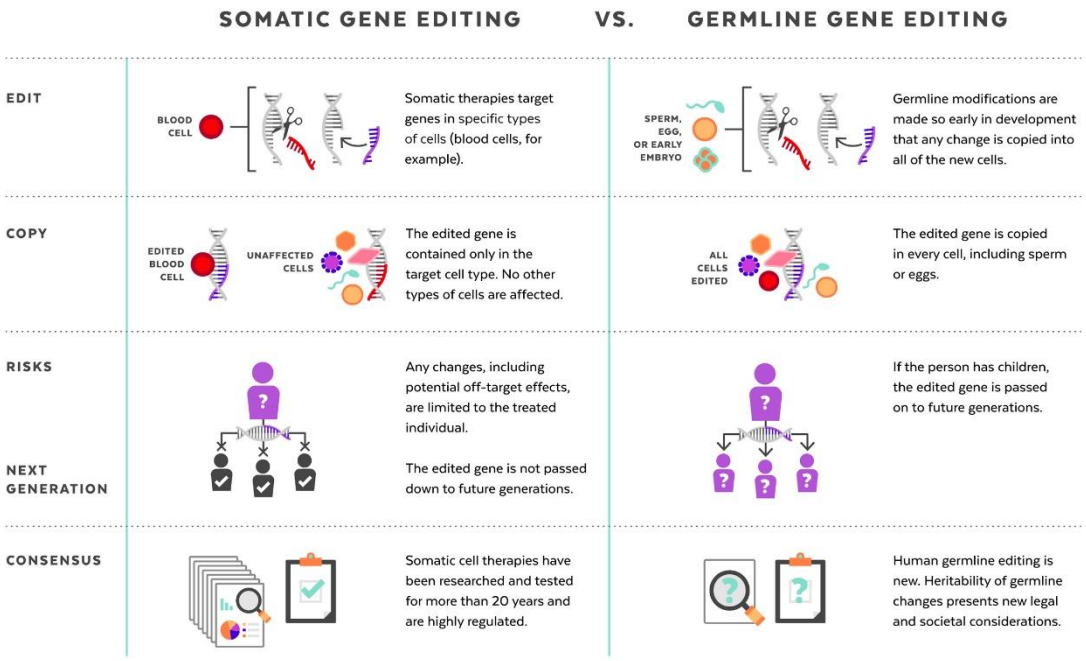

Figure 1: A comparison of somatic and germline gene editing[70]

To ameliorate TB, a delivery method that will achieve efficient and precise editing must be selected.[71] Unlike other diseases, TB may cause several genetic mutations. This was supported by a study conducted in Iran which identified eleven different mutations involved in the development of multi-drug resistant TB.[72] For gene therapy purposes, a single gene edit would be insufficient. Therefore, fulfilling this goal will require more efficient CRISPR delivery methods. To date, CRISPR delivery methods can be classified into in vivo, ex vivo and in utero.

[69] Mary Todd Bergman, 'Perspectives on Gene Editing' *The Harvard Gazette* (9 January 2019) <https://news harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/> accessed 30 December 2020.
[70] Ibid.
[71] Yip op cit note 66 at 6.
[72] Farhang Babamahmoodi and others, 'Evaluation of Gene Mutations Involved in Drug Resistance in Mycobacterium Tuberculosis Strains Derived from Tuberculosis Patients in Mazandaran, Iran, 2013' (2014) 3(3) *International Journal of Molecular and Cellular Medicine* 195.

a) *In vivo gene editing*

In vivo gene editing involves the direct delivery of CRISPR via vectors into the patient's body to directly treat its cells.[73] In vivo gene editing is most beneficial in circumstances where extracting and culturing the target cells outside the human body would be difficult.[74] Hirakawa and others identify that there are currently 'precision related' challenges with in vivo gene editing. They argue that the most attention-grabbing concern is the delivery issue: how can CRISPR be accurately delivered to the target tissue in a controlled manner thus limiting off-target effects?[75] This delivery issue is more pronounced when dealing with the treatment of TB as there is no direct access to the target tissue, which is why most in vivo clinical studies to date have concentrated on target tissues with direct access such as the cervix, the eye and the ear.[76]

However, Craig and Conlon also aver that the delivery vehicles for gene therapy and germline gene editing are likely to vary because in gene therapy, the DNA is delivered with to persist with the introduced DNA whereas in germline gene editing, the gene editor is only present long enough to achieve the correction.[77] That being the case, when performing gene therapy, viral vectors are more effective as they allow long-term expression.[78] Viral vectors are also used due to their inherent ability to penetrate cells, to insert a functional transgene and to compensate for an inherited mutant gene malfunction (gene replacement) or to activate a new role in altered cells (gene addition).[79] However, with germline gene editing, this may contribute to undesirable effects as the CRISPR enzyme will be continuously expressed. Conversely, non-viral vectors may allow a more controlled germline editing as viral vectors have proven to have low efficacy levels.[80]

b) *Ex vivo gene editing*

Unlike in vivo gene editing, ex vivo gene editing is currently the most promising delivery method as higher levels of editing can be achieved through it. In this gene delivery method,

[73] Karim Shalaby, Mustapha Aouida & Omar El-Agnaf, 'Tissue-Specific Delivery of CRISPR Therapeutics: Strategies and Mechanisms of Non-Viral Vectors' (2020) 21 *International Journal of Molecular Sciences* 5.
[74] Ibid 6.
[75] Matthew P Hirakawa and others, 'Gene Editing and CRISPR in the Clinic: Current and Future Perspectives' (2020) 40(4) *Biosciences Reports* 14.
[76] Ibid 14–15.
[77] Hodges and Conlon op cit note 65 at 104.
[78] Kenneth Lundstrom, 'Viral Vectors in Gene Therapy' (2018) 6 *Diseases* 42.
[79] National Academies of Sciences op cit note 68.
[80] V Thankur and others, 'Viral Vector Mediated Continuous Expression of Interleukin-10 in DRG Alleviates Pain in Type 1 Diabetic Animals.' (2016) 72 *Molecular and Cellular Neuroscience* 46–53.

target cells are removed from the body, edited, and then transplanted back into the host.[81] However, while the methods of ex vivo delivery seem promising, it is not sufficient for most genetic disorders because it is primarily restricted to diseases where edits can be made on adult stem cells, as it requires the cells to survive outside the body and to be susceptible to external manipulation and culturing.[82]

Accordingly, in this paragraph, I discuss the potential role of adult stem cells in treating infectious diseases via ex vivo gene editing, with a focus on TB. Mesenchymal Stromal Cells (MSCs) are adult progenitor cells found in the bone marrow and a number of other organs.[83] They are considered to be organ homeostasis and tissue repair facilitators following inflammation and/or tissue damage.[84] Because they are the key cells in connective tissue and are known to migrate to areas of lung injury, MSCs could therefore dampen inflammation associated lung damage in TB patients.[85] This supports the possibility that organ-damaging cascades in TB infections can be curbed with editing MSC cells. Most importantly, this also signifies that ex vivo gene editing for the treatment of TB is highly possible and is likely to yield good results by promoting tissue repair when reinfused in TB patients. For example, the most recent clinical study performed to insert a TB resistance gene — *NRAMP1*— into the cow genome was carried out ex vivo by injecting cells carrying the TB resistance gene into the egg cell of a female cow.[86]

Ex vivo gene editing can also be achieved by injecting directly into the embryo or zygote in vitro. Once gene editing has been carried out, the embryo is transferred into the woman's uterus, where it will continue its development. However, since editing an embryo's genome would be much easier if the embryo were conceived in vitro, pursuing the in vitro route would compel patents to give up natural in favour of assisted reproduction.[87] This is because it would not be necessary to go through the woman's body to modify the embryo.

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[81] Paul Ross, *Developing Novel Therapeutic Strategies for Rett Syndrome.* (Doctor of Philosophy, University of Glasgow, 2016) 40.
[82] Ibid 40–42.
[83] Ann-Kristin Afflerbach and others, 'Mesenchymal Stem Cells as a Promising Cell Source for Integration in Novel In Vitro Models' (2020) 10 *Biomolecules* 1306–1307.
[84] Shreemanta K Parida and others, 'Cellular Therapy in Tuberculosis' (2015) 32 *International Journal of Infectious Diseases* 32–33.
[85] Firoz Naem Khan, Kamal Uddin Zaidi & Vijay Thawani, 'Stem Cell Therapy: An Adjunct in the Treatment of MDR Tuberculosis' (2017) 3(3) *Journal of Stem Cell Research & Therapeutics* 260.
[86] Yang Zhang, 'Tuberculosis-Resistant Cows Developed for the First Time Using CRISPR Gene-Editing Technology' *Genome Biology* (February 2017) <https://www.biomedcentral.com/about/press-centre/science-press-releases/01-02-17> accessed 3 December 2020.
[87] Maurizio Balistreri, 'Genome Editing, Human Cloning, In Vitro Gametes and Artificial Womb: Towards Future Scenarios, New Dilemmas and Responsibilities.' (2018) 20(3) *Ethics & Politics* 18.

c) *In utero gene editing*

In utero gene editing presents the opportunity to remedy the target disorder before birth and the onset of symptoms.[88] The rationale for in utero gene editing involves the small size of the foetus, and the availability of numerous organ stem/progenitor cells that are highly proliferative.[89] This is very beneficial for diseases with high perinatal morbidity and mortality such as TB and for which there are no sufficient postnatal therapies. The possibility of in utero gene editing necessitates the need to understand the burden of childhood TB and the potential impact of offering in utero gene editing.

While TB is the leading cause of death amongst all age groups, pneumonia is the number one cause of death among children below the age of five. In 2013, it was estimated to have caused 935,000 deaths in children under five years.[90] However, although under-diagnosed — due to problems with the diagnosis of TB in children as stated earlier — TB has been recognised as the cause of Pneumonia in children especially in areas with high TB prevalence.[91] A recent study found that TB was also present in between one per cent and twenty three per cent of childhood pneumonia cases.[92] These studies have highlighted that although rates of childhood TB infections loom high, TB is highly undiagnosed in children and usually left untreated. TB is therefore likely to be one of the major causes of mortality for under-fives than is generally assumed.[93] Accordingly, remedying the challenge of undiagnosed childhood TB through in utero gene editing is essential to avoid millions of avoidable deaths among children.

More so, a major impediment to the clinical translation of CRISPR-CasX for the treatment of TB, as previously discussed, is the absence of suitable in vivo delivery methods to deliver CRISPR to the target tissue. Much reliance has been placed on ex vivo germline editing which enables the edited cells to be re-implanted back into the patient. Accordingly, the accessibility and proliferative nature of progenitor or stem cells of most organs is perhaps the greatest advantages of performing in utero gene editing for the treatment of TB.[94]

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[88] Heather A Hartman, Avery C Rossidis & William H Peranteau, 'In Utero Gene Therapy and Genome Editing' *Current Stem Cell Reports* 54.
[89] William H Peranteau & Alan W Flake, 'The Future of In Utero Gene Therapy' (2020) 24 *Molecular Diagnosis & Therapy* 135.
[90] Helen E Jenkins, 'Global Burden of Childhood Tuberculosis' (2016) 8(24) *Pneumonia* 1.
[91] Ibid 2.
[92] JN Oliwa and others, 'Tuberculosis as a Cause or Comorbidity of Childhood Pneumonia in Tuberculosis-Endemic Areas: A Systematic Review' (2015) 3(3) *Lancet Respir Med* 235–243.
[93] Ibid 5.
[94] Hartman, Rossidis & Peranteau op cit note 88 at 53.

However, any prenatal intervention presents the risk of not only affecting the developing foetus but also the mother. [95] Central to the continuous development of fetoscopy and foetal surgery, is the need that in-utero germline editing should be performed with minimal trauma and invasion.[96] Accordingly, any in utero gene editing delivery vehicles would have to be optimised to minimise such exposure to risk while also accomplishing efficient gene editing. There are two main routes of administration that can be considered for foetal germline editing. That is, administration into the foetal circulation and administration into the amniotic cavity.

i. *System delivery through foetal circulation*

In this delivery method, the umbilical vein is used to enter the foetal circulation.[97] Thus, the expectant mother would be anaesthetised by an intra-muscular injection and thereafter CRISPR would be delivered into the placenta via laparoscopy (also known as keyhole surgery). This is a surgical procedure in which small incisions—about 1 to 1.5cm — are made on the abdomen to allow insertion of a laparoscope which relays clear images of the abdominal area to a television monitor thereby enabling the surgeon to carry out the required treatment.[98] CRISPR is therefore injected into the placenta and transferred to the foetus through maternal-foetal circulation as shown in the figure below.

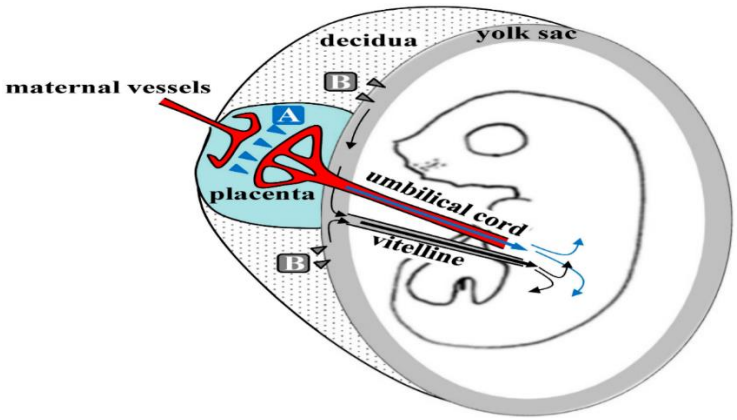

Figure 2: illustrating transplacental gene editing.[99]

[95] Deepthi Alapati and others, 'In Utero Gene Editing for Monogenic Lung Disease' (2019) 11(488) *Science Translational Medicine* 10.
[96] Anne-Marie Douar, Michael Themis and Charles Coutelle, 'Fetal Somatic Gene Therapy' (1996) 2(9) *Molecular Human Reproduction* 636.
[97] Shingo Nakamura and Satoshi Watanabe, 'Transplacental Gene Delivery (TPGD) as a Noninvasive Tool for Fetal Gene Manipulation in Mice' (2019) 20 *International Journal of Molecular Sciences* 7.
[98] Tehemton E Udwadia, 'Single-Incision Laparoscopic Surgery: An Overview' (2011) 7(1) *Journal of Minimal Access Surgery* 1.
[99] Shingo Nakamura and Satoshi Watanabe, 'Transplacental Gene Delivery (TPGD) as a Non-invasive Tool for Fetal Gene Manipulation in Mice' (2019) 20 *International Journal of Molecular Sciences* 8.

ii. *Intra-amniotic delivery*

Germline editing by intra-amniotic injections may be performed using the laparoscopy procedure as demonstrated above.[100] In terms of its safety, foetal surgeons and foetal medicine physicians have safely accessed the amniotic cavity for different medical procedures under ultrasound guidance.[101] These procedures have since the 1980's been used in clinical practice and carry a low risk of foetal loss.[102] Accordingly, a similar procedure could be used to safely deliver CRISPR , in utero as illustrated in the figure below. Developing foetuses are known to swallow amniotic fluid to aid in the formation of the gastrointestinal tract.[103] Thus, for purposes of this study, corrective genes injected into the amniotic fluid can, via normal foetal swallowing and breathing movements, reach the epithelium of the foetal lungs.[104] This is possible because the epithelial cells lining the intestine and lung only start differentiating towards the end of gestation. The figure below illustrates intra-amniotic method of gene editing.

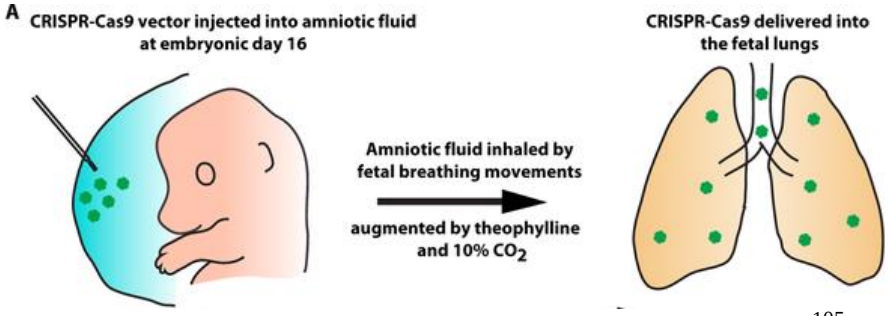

Figure 3: Intra-amniotic delivery of CRISPR-Cas9 results in pulmonary gene editing [105]

iii. *Optimal time of intervention*

As highlighted in the chapter, the gestational age of the foetus may affect the efficacy of gene editing, particularly germline. This has been demonstrated in studies whereby the lungs of

[100] Anne M Douar and others, 'Fetal Gene Delivery in Mice by Intra-Amniotic Administration of Retroviral Producer Cells and Adenovirus' (1997) 4 *Gene Therapy* 885.
[101] Adele S Ricciardi and others, 'In Utero Nanoparticle Delivery for Site-Specific Genome Editing' (2018) 9 *Nature Communications* 2.
[102] ibid.
[103] Ricciardi and others op cit note 101 at 2.
[104] Janet E Larson and Craig J Cohen, 'In Utero Gene Therapy' (2000) 2(2) *The Ochsner Journal* 108.
[105] Alapati and others op cit note 95 at 19.

rhesus monkeys were injected at different stages of development to treat different pulmonary illnesses. Results illustrated that several other organs were transduced when gene therapy was performed in the first trimester. Whereas gene therapy performed in the second trimester resulted in transgene expression that was more confined to the lungs.[106]

The results of the study therefore illustrate that in gene therapy, increased gestational age allows for precise organ-specific gene expression.[107] However, several factors can also equally compromise effective gene expression in much older foetuses. These factors include decreased number of proliferating cells system, maturation of the immune system and the increasing body mass.[108] For instance, if gene therapy is performed at a very late stage—beyond the beginning of the second trimester —, the corrective gene may only reach the trachea.[109] Also, since the human immune system is acquired progressively, performing foetal gene editing at a very late stage raises the possibility of immune responses to the vector and may trigger an inflammatory response instead.[110]

In terms of germline editing, studies have indicated that transfection of the germline cells in human foetus is unlikely via intra-amniotic delivery after seven weeks gestation.[111] This is because at seven weeks, the primordial germ cells migrate to the gonads (reproductive organs).[112] On average, the earliest one can tell if they are pregnant—through natural conception— is at 3–4 weeks. Therefore, to have an effective intra-amniotic method of germline editing, the expectant mother only has a 3–4 weeks window period from the time she discovers she is pregnant, to have the procedure performed.

Thus, this entails several factors as mentioned above must be considered when determining the optimal window period for in utero foetal gene editing. The window period appears to be much broader for gene therapy although gene therapy also appears to be more precise if performed in the second trimester. Conversely, the ideal time for germline editing via amniotic cavity, appears to be before the end of seven weeks — mid first trimester. Regrettably, there appears to be insufficient literature on the optimal time for germline editing via foetal circulation. However, the period would appear to be larger as the vector is injected directly into

[106] Simon N Waddington and others, 'In Utero Gene Therapy: Current Challenges and Perspectives' (2005) 11(5) *Molecular Therapy* 669.
[107] ibid.
[108] ibid.
[109] Larson and Cohen op cit note 104 at 108–109.
[110] Douar, Themis & Coutelle op cit note 100 at 638.
[111] Larson & Cohen op cit note 104 at 108.
[112] ibid.

the bloodstream making it possible to reach even the gonads — beyond seven weeks of gestation — thereby enabling germline transduction.

V. ETHICAL ISSUES RELATING TO GENE EDITING

Human gene editing may one day stop the transmission of some serious genetic illnesses from parents to their offspring by the deliberate changes in the DNA sequence using CRISPR-CasX. Eliminating dreadful diseases that cause agony, death, and resource depletion from the future generations seems like an unquestionable goal, however, with it also comes some degree of risks of harm not only to individuals born of the technology, but also to their future generations.[113] It is therefore often argued that human genome editing could have adverse effects on the individual who is the subject of the intervention, notwithstanding any apparent advantages. The main concern in this case is that the inherent risks of human genome editing are greater than those of regular medical procedures due to how genes function.

As such, Persson and Savulescu perceptively point out that human genome editing may be more harmful than beneficial because it involves a transformation of a complex system. Tampering with a complex nature like the human genome is 'more likely to be for the worse rather than for, the better.'[114] Hence, Brock argues that even in its therapeutic form, human genome editing is a special kind of technological intervention because its effects would not only be passed on to the treated patient but also to their progeny who never consented to the harm therefore if its safety has not been fully demonstrated it might be worth holding off on germline genetic manipulations until safety is proven.[115] Ying-Qi further argues that the real subjects of human genome editing are in fact the resultant children who will be born from the edited genomes and bear the repercussions of the treatment, not the parents.

In such a situation, it is essential to appropriately take into account children's interests to prevent them from being exploited as a crutch to defend dubious technologies like human genome editing.[116] In properly positioning children in the current human genome editing

[113] KR Smith, S Chan and J Harris, 'Human Germline Genetic Modification: Scientific and Bioethical Perspectives' (2012) 43 *Archives of Medical Research* 504.
[114] Ingmar Persson and Julian Savulescu, *Unfit for the Future: The Need for Moral Enhancement* (Oxford University Press 2012) 116.
[115] DW Brock, 'Enhancements of Human Function: Some Distinctions for Policymakers', *Enhancing Human Traits: Ethical and Social Implications* (Georgetown University Press 1998) 62.
[116] Ying-Qi Liaw, 'A Child-Centred Approach in Human Heritable Genome Editing' (PhD thesis, Newcastle Law School 2021) 11.

discussions, ethical justifications that are children-centred can be mapped by exploring the non-identity problem, which is later discussed in Chapter 5 of the thesis. The subject of future (unborn) children immediately raises a philosophical contradiction, known as the non-identity problem, which underscores the difficulties in defending ethically dubious actions when the child depends on those actions for his or her very existence.[117] As will be demonstrated in the chapter, the non-identity problem fails to adequately safeguard children's interests. The non-identity problem seems to imply that there should be no restrictions on human genome editing as long as its use results in the existence of the child as compared to non-existence (apart from exceedingly rare circumstances in which life is not worth living).

In assessing the risks of gene editing, although DNA sequences can be modified using CRISPR/Cas, one drawback is the possibility of linked off-target effects.[118] Off-target CRISPR effects are inadvertent editing occurring at unintended genomic locations that share genetic characteristics with the targeted location. Reports that CRISPR/Cas tool use involves a danger of unintentional mutagenesis at closely matched genomic sequences emerged soon after it was discovered that the mammalian genome could be modified using this technology.[119] The pleiotropic character of genes suggests that it may be challenging for researchers to predict the outcome of a specific genetic intervention, as the majority of genes appear to have more than one function and affect more than one bodily function.[120] I wish to draw attention to a case cited by Coors in which genetic modification in mice led to the *p53* gene overexpression. Although this treatment decreased the mice's risk of developing cancer, it also markedly shortened their life span.[121] This illustrates that human genome editing could have wholly unforeseen repercussions for other bodily functions that were not at all suspected to be related to the function of the gene.

This is among the causes for which scientist He's experiment drew harsh criticism for being premature.[122] In 2019, a Chinese scientist named Jian-kui HE claimed to have created the first gene edited babies whose CCR5 genes were altered to make them naturally immune

[117] Derek Parfit, *Reasons and Persons* (Oxford University Press 1984) 359.
[118] Dominik Modrzejewski and others, 'Which Factors Affect the Occurrence of Off-Target Effects Caused by the Use of CRISPR/Cas: A Systematic Review in Plants' [2020] *Frontiers in Plant Science*.
[119] Benjamin Davies, 'The Technical Risks of Human Gene Editing' (2019) 34(11) *Human Reproduction* 2104, 2105.
[120] ME Coors and L Hunter, 'Evaluation of Genetic Enhancement: Will Human Wisdom Properly Acknowledge the Value of Evolution?' (2005) 5(3) *The American Journal of Bioethics* 21.
[121] ibid 21–22.
[122] Jing-ru Li and others, 'Experiments That Led to the First Gene-Edited Babies: The Ethical Failings and the Urgent Need for Better Governance' (2019) 20 *Journal of Zhejiang University Science* 32.

to the human immunodeficiency virus (HIV).[123] The announcement immediately sparked intense criticism, condemnation, and discussion regarding the validity of HE's genetic research from a scientific and moral standpoint. More so, the inheritability of germline genetic interventions is another aspect that made He's research extremely contentious. The gene edited twins—nicknamed Lulu and Nana — born as a result of scientist He's experiment were purportedly exposed to a high risk of off-target effects.[124]

Put succinctly, the CRISPR/Cas tool may therefore cause deleterious off-target effects at the genomic level. These mutations usually involve a single-nucleotide insertion or deletion, which is often of a small size. Nevertheless, larger deletions do occasionally occur, and these unforeseen large deletions have the potential to either eliminate a gene or incorrectly regulate surrounding expressed sequences.[125] Accordingly, these findings emphasize the necessity for scientists utilizing CRISPR-CasX to be aware of and test for these potential unexpected outcomes. This is even more important if scientists want to use the technology in healthcare because unintentional genetic changes like this could cause illnesses like cancer.[126] This has been backed by a recent study that performed numerous runs of conventional CRISPR/Cas9 in various human cell lines. The study revealed that, although it only happened five or six per cent of the time in the study's experimental model, the use of CRISPR raised the possibility of significant DNA rearrangements which may cause cancer.[127] CRISPR appears to exacerbate a natural process — retro transposition — in which DNA sequences referred to as 'jumping genes' replicate and migrate from one spot in the genome to another. Even though retro transposition is normally harmless, jumping genes have been associated to diseases such as haemophilia and cancer.[128]

More so, the detection of off-target sites in a thorough and highly sensitive manner continues to be a major obstacle in the field of gene editing.[129] Although there have been

[123] ibid 32–33.
[124] ibid 35.
[125] Davies op cit note 119 at 2106–2107.
[126] University of Cambridge, 'Researchers Call for Greater Awareness of Unintended Consequences of CRISPR Gene Editing' <https://www.cam.ac.uk/research/news/researchers-call-for-greater-awareness-of-unintended-consequences-of-crispr-gene-editing-0> accessed 17 October 2022.
[127] Nancy Fliesler, 'A Potential Danger of CRISPR Gene Editing — and Why Base Editing May Be Safer' *Boston Children's hospital* <https://answers.childrenshospital.org/crispr-gene-editing/#:~:text=They%20found%20that%20CRISPR%20increased,rearrangements%20can%20theoretically%20trigger%20cancer.> accessed 18 October 2022.
[128] A Movafagh, 'The Role of Transposable Element or Jumping Genes in Cancers' (2016) 1(4) *Asian Pacific Journal of Cancer Biology* 76.
[129] Xiao-Hui Zhang and others, 'Off-Target Effects in CRISPR/Cas9-Mediated Genome Engineering' (2015) 4 *Molecular Therapy - Nucleic Acids* 4.

advancements in advanced off-targeting detection techniques, these have largely been successful in silico and in vitro. These detection techniques are unable to accurately detect mutations that take place in vivo, therefore necessitating the need to develop effective ways to identify the in vivo sites of the off-target mutations.[130]

What is clear is that any unanticipated off-targeting events resulting from the technology's clinical application could have an irreversible intergenerational effect — human genome editing can introduce unintended mutations which are passed on to the next generation. Unexpected off-targeting incidents indicate that the technology should be thoroughly evaluated and reviewed before being put into use.[131] Hence, in 2020, the National Academy of Sciences advised against the use of genetically altered human embryos for fertilization, stating that this should wait 'unless and until it has been clearly established that it is possible to efficiently and reliably make precise genomic changes without undesired changes in the embryos.'[132] As such, consequentialist arguments against human genome editing hold that there are negative consequences which are likely to follow, and as these consequences are ethically undesirable, we should refrain from developing and utilising this technology.

Naeem et al however aver that selecting *Cas* variants is a possible way to minimize off-target effects.[133] The native CRISPR-Cas9 endonucleases are known to tolerate mismatches.[134] That is, they have an inability to distinguish between the target sequence and extremely similar sequences. In order to improve therapeutic gene editing with minimal off-target effects, researchers are therefore striving to develop modified Cas9 variants with increased on-target-binding selectivity and decreased off-targets.[135] The development of these improved primary editing methods gives hope for the possibility of genetic diseases with minimum off-target effects in human cells. By utilising cutting-edge genomics techniques and thoughtfully planned

[130] ibid.
[131] Kayla Carey, Junghyun Ryu and Kyungjun Uh, 'Frequency of Off-Targeting in Genome Edited Pigs Produced via Direct Injection of the CRISPR/Cas9 System into Developing Embryos' (2019) 19(25) *BMC Biotechnology* 2.
[132] National Academy of Science, National Academy of Medicine and The Royal Society, 'Report Summary: Heritable Human Genome Editing' 7 <https://www nap.edu/resource/25665/Heritable%20Human%20Genome%20Editing%20Report%20Summary%20-%20FINAL%2020200903.pdf> accessed 1 July 2021.
[133] Muhammad Naeem and others, 'Latest Developed Strategies to Minimize the Off-Target Effects in CRISPR-Cas-Mediated Genome Editing' (2020) 9(7) *Cells* 1608, 1623.
[134] Mark Thomas, Gaetan Burgio & David J Adams, 'Collateral Damage and CRISPR Genome Editing' (2019) 15(3) *PLoS Genet*.
[135] Naeem and others op cit note 133 at 1623.

experiments, we can enhance our methods for verifying edited cells while also learning more about the effects of CRISPR-Cas editing in vivo.[136]

However, Thomas et al note that by creating a Cas variant with this greater specificity, its overall activity may be diminished in some sgRNA targets as a target region may impose certain restrictions and it might not always be possible to choose sgRNAs with few off-targets.[137] They suggest that while these recommendations aim at lessening the negative consequences of human genome editing, it will ultimately be preferable to prevent *in vivo* editing wherever possible in future therapeutic applications. Cells from the patient should be edited in a lab setting using an *ex vivo* method. It is only after thorough genotyping is undertaken to confirm that no unwanted mutations or off-target consequences have occurred, that these cells should be returned to the patient.[138]

Accordingly, this calls for caution when it comes to the modification of human embryos because unintended mutations might have negative effects on the person and, in some situations, future generations. It however appears that the therapeutic use of the technology to eradicate or stop the spread of genetic disorders, appears to be a prevalent and more palatable justification for its usage in clinical settings.[139] Nuffield draws attention to the fact that in-depth studies on genome editing methods are currently being conducted with the goal of enhancing human health. Although it points out various drawbacks on the use of the technology, such debate undoubtedly suggests that enhancing human health — a therapeutic objective— would be a respectable ethical justification for the use of CRISPR-CasX in emolliating disease.[140] However, the claim of therapeutic use for human genome editing, according to Rulli, is erroneous and misleading.[141] She argues that the options for parents in human genome editing applications are not just whether to use human genome editing to have a child who is genetically healthy or not to use human genome editing with a child who might be born with specific genetic diseases; there is also another option for the parents, which is to not have a child at all. Thus, in light of the fact that human genome editing entails creating a child with

[136] Ida Höijer and others, 'CRISPR-Cas9 Induces Large Structural Variants at on-Target and off-Target Sites in Vivo That Segregate across Generations' (2022) 13(627) *Nature Communications.*
[137] Thomas M, Burgio G and Adams DJ, 'Collateral Damage and CRISPR Genome Editing' (2019) 15(3) *PLoS Genet* 3.

[138] ibid 6.
[139] Liaw op cit note 116 at 12.
[140] Nuffield Council on Bioethics (Nuffield), Genome Editing: An Ethical Review (Nuffield Council on Bioethics 2016).
[141] Tina Rulli, 'Reproductive CRISPR Does Not Cure Disease' (2019) 33 *Bioethics* 1072.

particular desired features (such avoiding certain genetically connected illnesses), it is proposed that it is more reproductive than therapeutic.[142]

Furthermore, even if it was acceptable that human genome editing is therapeutic, it is debatable whether its designation as a 'treatment' can credibly establish an ethical barrier in determining the technology's clinical acceptability. Another way to debate the application of human genome editing is to identify the technological applications for therapy and enhancement in addition to creating a line between somatic and germline editing. Enhancement may be defined to mean improving 'normal' human bodily functions or human capacities, while therapy may be defined as the process of treating people who have diseases or impairments with the goal of returning them to a normal level of health and fitness. [143] It is hence suggested that 'therapeutic' uses of human genome editing fall under medical objectives whereas enhancement does not. In support of this, scientist He seemed to have accepted this distinction when he expressly said that he is against enhancement as such use is morally dubious. In the panel discussion during the Second International Summit, He made an effort to distance himself from the 'enhancement' usage of human genome editing when responding to the worry that the edited CCR5 gene in the CRISPR babies may have enhancement impacts on cognitive function of the twins.[144] McKeown argues the distinction between therapy and enhancement is based on the fallacious premise that health, disease, and normality can all be accurately defined, but in reality, all of these notions are highly subjective and hence open to different interpretations.[145] Dupre cautions us that a person's cultural and technological background determines what is considered as normal. He gives an example of how deaf persons could be perceived as abnormal in a non-deaf environment but as normal in a deaf community.[146] Therefore, it may be claimed that a person's normality depends on the context to which they belong. Similarly, depending on the severity of TB cases and deaths in a given country, the use of human genome editing for TB prevention as may qualify as either enhancement or therapy.

Resnik further argues that this distinction has no moral importance as not all medical therapy is intrinsically morally acceptable and not all forms of enhancements are morally

[142] ibid.
[143] David Resnik, 'The Moral Significance of the Therapy-Enhancement Distinction in Human Genetics' (2020) 9 *Cambridge Quarterly of Healthcare Ethics* 365.
[144] Liaw op cit note 116 at 14.
[145] Alexander James McKeown, 'Re-Thinking the Distinction between Therapy and Enhancement: A Study in Empirical Ethics' (PhD thesis, University of Bristol 2013) 7.
[146] John Dupre, 'Normal People' (1998) 65 *Social Research* 234.

problematic.[147] Ying-Qi avers that a good example of the ambiguity between therapy and augmentation is the vaccination instance. The primary purpose of vaccinations is to strengthen the immune systems of the individuals in order to protect them against a variety of illnesses. This forces us to make one of two decisions: (1) acknowledge that immunizations belong under medical territory and are hence regarded as therapy; or (2) argue that vaccination is an exceptional kind of enhancement, demonstrating that not all forms of enhancement are morally problematic.[148] Accordingly, Chapter 2 of the thesis discusses how the International Commission on the Clinical Use of Human Germline Genome Editing's classifies other uses of human genome in the same category as genetic enhancement thus emphasising the blurry line in drawing a distinction between human genome editing for disease prevention and enhancement.

Another frequently voiced concern of human genome editing is that unequal access to these technologies may worsen social and global disparities and result in injustices. The framing notion is that human genome editing primarily benefits the individual and that this advantage should be weighed against the potential social or collective harms.[149] The possibility of modifying the human genome to remove disabling traits seems captivating – how could anyone oppose it? The idea of autonomy has bleak resonances when debating about the permissibility of human genome editing. The crux of the issue relates to how one adjudicates between individual interests of a person seeking to make use of the technology to remedy a disease or for enhancement and the presumed interests of the community he or she resides in. For instance, Gardner avers that if these genetic interventions give people advantages in competitions for social goods such as wealth, status, or power, this improved capacity for competition will consequently increase the variance of the distribution of social goods, contributing to the widening gap between the well-off and the less-so.[150] Baruch et al also argue that human genome editing would have a detrimental impact on the dignity and broader societal perceptions against persons with disabilities for instance by regarding them as 'problems' that could have been prevented by placing burdensome expectations on parents to have genetically perfect children.[151] Similarly, Pollack depicts that the pessimistic

[147] Resnik op cit note 143 at 374.
[148] Liaw op cit note 116 at 16.
[149] A Buchanan, *Beyond Humanity? The Ethics of Biomedical Enhancement* (Oxford University Press 2011) 36.
[150] W Gardner, 'Can Human Genetic Enhancement Be Prohibited?' (1995) 20(1) *The Journal of Medicine and Philosophy* 69–74.
[151] Susannah Baruch and others, *Human Germline Genetic Modification: Issues and Options for Policymakers* (Johns Hopkins University Berman Institute of Bioethics 2005) 7.

outcome of germline editing is that those who choose not to have their genes modified or persons who are subsequently born with an avoidable disease would live in an environment with a complexity of genome different from what the technology will be able to define as 'normal'.[152]

VI. PROBLEM STATEMENT

Although notable progress has been made by South Africa in TB control, the burden of TB remains a priority national health issue. TB treatment outcomes are improving at a very slow rate. Despite that the current TB treatment regimens have existed for decades, they do not address the special needs of certain groups most vulnerable to TB. South Africa has a diverse population and an extraordinary variety of TB strains. Hence, the present inability of antibiotics to permanently treat TB indicates the need for an enhanced approach to combat the illness by heeding genetic variations among the different South African populations. This entails considering the genetic disposition of South Africans and their susceptibility to TB in formulating-appropriate TB treatment to accelerate the progress towards TB elimination. Put differently, the distinctive combination of host genomes of a specific population and the prevailing pathogen must be considered. Owing to the genetic complexity of TB and the compounding financial implications current TB medication has on our health budget, it is pertinent to shift away from the underlying assumption that the TB problem can be solved through existing biomedical tackles alone.[153]

Therefore, additional efforts are needed to reach the End TB Strategy and SDG targets for 2030. Consequently, analysing the treatment of TB though human right lenses can improve states' obligations and their health systems' responses to TB.[154] Access to medicine implies that the state must provide adequate and quality healthcare facilities that are available to all. The South African Constitution proclaims and protects the right of access to healthcare. Section 27 expressly guarantees the right to access medicine and healthcare services. Paragraph 12 of General Comment No. 14 clarifies that there are five vital components in the right to health which are legal enforceability, accessibility, availability, acceptability, and quality.[155]Among the above challenges stands the uncertainty towards the ambit of this Constitutional

[152] Adam Conti, 'Drawing the Line: Disability, Genetic Intervention and Bioethics' (2017) 6(9) *Laws* 5.
[153] KK Holmes, S Bertozzi & BR Bloom, *Major Infectious Diseases* Washington DC: The World Bank, (2017) 200.
[154] Frick, Henry and Lessem op cit note 35 at 15.
[155] General Comment No. 14, E/C.12/2000/4 (2000) available at https://tbinternet.ohchr.org/_layouts/15/treatybodyexternal/Download.aspx?symbolno=E%2fC.12%2f2000%2f4&Lang=en, accessed 16 July 2019.

commitment to ensure that all South Africans have access to healthcare services such as human genome editing. Paying attention to this socio-economic right is crucial in ensuring South Africans expect access to progressive medical innovations such as gene editing to avert the TB epidemic. The realisation of the use of gene-editing technology, such as CRISPR-CasX, to treat medical ailments such as TB is therefore dependent on the interpretation of the right of access to healthcare.

This study is therefore different from previous studies because the advance of human heritable genome editing over the decades has been overshadowed with theoretical ethical debates due to substantial technical risks and uncertainties concerned. However, the recent birth of CRISPR genome-edited twin babies in China highlights a substantial oversight question in the heritable human genome editing debate. Relevant is the need to consider not whether such technology can be offered in human reproduction, but rather, if such technology is required, what rights could be promoted to assure access to the technology. Taking into account the severity of the TB epidemic in South Africa, this thesis addresses the question of whether and how the right of access to healthcare services and other interrelated rights can provide a sound basis for demanding access to heritable human genome editing as a legal right in the search for a suitable treatment for TB in South Africa. To that end, the study is nested within the broader context of South Africa's legal, political and economic limitations in respect of the subsequent realisation of the right to access healthcare services. The study is therefore novel in that it investigates the legal questions related to the use of heritable human genome editing from a health rights perspective specifically for the treatment of TB.

With the pace at which gene-editing technology is developing, the debut of CRISPR-CasX creates new opportunities for effective TB treatment. The constraints of current TB medications leave patients dependent on long, intolerable regimens that often trigger adverse effects on the patients, making adherence tough and creating circumstances under which drug-resistant strains may thrive. Therefore, apart from requiring new TB policies, turning the tide against TB will likely require advances in technology to accelerate a cure and prevent TB.[156] Hence, advocating heritable human genome editing from a health rights approach entails constant exploration and consideration of the most up-to-date medical knowledge and benefiting from such scientific progress.

[156] Holmes, Bertozzi and Bloom op cit note 153 at 238.

As such, this study also acknowledges that the right to science has an instrumental value to access to medical advancements like human genome editing in South Africa. Although there is growing momentum on the inclusion of human rights in TB programmes, little has been done to explore the application of the right to science and to benefit from such scientific advancements. This study therefore also examines the extent to which right to science may contribute to the realisation of the right of access to gene editing technology. Against this backdrop, the study sought to give an answer to the question: how does the right to science enhance access to gene editing technology?

Furthermore, in a hypothetical attempt by the government to curb TB with the use of gene-editing technology particularly CRISPR-CasX, such initiatives may be confronted with a number of ethical issues. Due to safety and technological concerns associated with CRISPR-CasX, there are still many unknowns surrounding the therapeutic uses of human genome editing. Put differently, due to the fact that germline editing is heritable, there are risks involved for not only the persons who utilize it now but also for generations to come.[157] This, according to Lanphier et al, renders it 'dangerous and ethically unacceptable.'[158] The ability of humans to make alterations to genes using gene-editing technology consequently raises safety concerns of CRISPR and rights of future generations. But just because a procedure is potentially dangerous does not automatically mean that we should completely disregard it, especially if it has significant potential benefits. One can agree that human genome editing might help the intended subject while at the same time believing that its use would be detrimental to society as a whole.

That being the case, what level of caution should be applied when using this novel technology? While future generations are not typically given a voice in legal debates, they do have an audience in policy, or ethical debates. In reaction to this, the study will therefore also analyse the precautionary principle and the theory of intergenerational justice. The problematic aspect with the theory of intergenerational justice lies in whether it is reasonable to say that we have obligations to individuals who do not yet exist and that by editing our genes we are infringing on their rights.

[157] Michaela Rae Steytler, 'The Right to Freedom of Scientific Research in the Age of Gene Editing' (LLM thesis, University of Kwazulu-Natal 2020) 110.
[158] E Lanphier, F Urnov & SE Haecker, 'Don't Edit the Human Germline' (2015) 519 *Nature* 410.

VII. OBJECTIVES

Given the problem set out above, the primary question this thesis seeks to answer is: Does the South African Constitutional right of access to healthcare services, include the right to human genome editing technology such as CRISPR-CasX for treating TB?

The thesis aims to address the following objectives:

1) To analyse the right of access to healthcare in the context of gene-editing technology.
2) To appraise South Africans in demanding access to gene-editing services as a legal right in the search for a suitable treatment for TB.
3) To analyse the instrumental value of the right to science to enhance access to health technologies
4) To determine how in pursuant of the theory of intergenerational justice the rights of the present generation may be properly balanced with those of the future generation.

5) To determine the current international trends in applying the precautionary principle in the regulation of human genome editing and how South Africa should proceed to apply the precautionary principle.

VIII. RESEARCH METHODOLOGY

This study is a doctrinal legal study. The researcher relied on primary and secondary data sources, such as the South African Constitution with particular emphasis on section 27 as well as case law regarding socio-economic rights. The analysis of these cases formed the bedrock of this study. The researcher also made use of other reliable internet sources, in particular, websites of international organisations such as the World Health Organisation (WHO) for purposes of accurate health-related statistics needed for this research. The study also referred to textbooks and journal articles relating to the right of access to healthcare services. These journal articles and textbooks were accessed from internet sources and the library. The study also includes data collected and analysed from a 2021 Deliberative Public Engagement survey on South Africans' views and attitudes on heritable human genome editing.

IX. STRUCTURE OF THE THESIS

This study is organised into six chapters and are outlined as follows:

Chapter one: Introduction

This chapter sets out the background of the study and gives a detailed outline of the research problem. As an introductory chapter, this chapter also sets out the objectives of the study and the research methodology adopted. This chapter also reviews the current scientific technology (CRISPR-CasX) and its potential use in the treatment of TB.

Chapter two: The right to science

This chapter explores the right to science in enhancing TB treatment research. Since the right to benefit from scientific progress is not expressly provided for in our Constitution, the chapter discusses how other rights may be interpreted to give effect to the right to benefit from scientific progress.

Chapter three: Should we be cautious in promoting the right to human genome editing for treating TB?

Chapter three discusses a potential limitation on the use of gene-editing technology. Since gene-editing technology carries a degree of risk of harm, the chapter discusses how such risks may pose a threat to public health. In the need to strike a balance between the benefits of gene-editing technology and the need to avert such risks of harm, a discussion on the precautionary principle ensues. The chapter also recommends how South Africa should proceed to apply the precautionary principle. This study formulates a version of the precautionary principle that best serves South Africa's healthcare needs while minimising harm to its people. This is achieved by considering the values underpinning the Constitution in paving a way for a more workable solution in addressing South Africa's TB epidemic

Chapter four: A right to access to heritable human genome editing in South Africa

Chapter four undertakes an extensive analysis of the ambit of the right to have access to healthcare services as enshrined in the South African Constitution. In doing so, the chapter first investigates how the right to health under international instruments has been interpreted. This chapter also discusses South African jurisprudence on the extent to which the courts have given the normative and substantive content to the right of access to healthcare services to establish its ambit. For the most part, these cases were studied to shed light on concepts such as 'available resources' and 'reasonable measures' as provided for under section 27. In the context of the

development of gene-editing technology and TB, this chapter makes a case for the right to heritable human genome editing in South Africa.

Chapter five: The theory of intergenerational justice: Serving health justice for all generations?

A theory of intergenerational justice involves the study of the moral status of the relations between present and future people, more specifically, of the obligations and entitlements they can potentially generate. This chapter discussed to what extent the current generation should have regard to the interests of the future generation. Most importantly it answers the question whether human genome editing could constitute an infringement on the rights and/or interests of the future generation.

Chapter six: Conclusion

This comprises of the recommendations and conclusion of the study.

CHAPTER 2

THE RIGHT TO SCIENCE

'I know it's a long shot and people would say it's "too absurd" ... but I'm doing this with hopes of making a Mickey Mouse someday.' **- Arikuni Uchimura**

I. SETTING THE SCENE: SCIENCE AS A RIGHT

The right to science is one of the oldest rights to be recognised internationally in the Universal Declaration of Human Rights (UDHR). The right to science as commonly known includes both the right of scientific research and the right of everyone to benefit from scientific progress and its applications.[1] The genesis of this right can be traced back to the Second World War (WWII). Nuclear bombing and many other weapons of mass destruction were among the fruits borne by the idea of science serving the state. To be more precise, the ability of Americans to annihilate cities using nuclear bombs was all made possible through science.[2] With these bitter lessons in mind, the UDHR conveyed a vision that science should be at the service of humanity. In other words, science should adhere to high ethical standards and should only be used to alleviate human suffering and to improve mankind.[3]

The relevant provision of the UDHR reads as follows:

'Article 27.

1. Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits.
2. Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author.'

A similar vision emerged after the establishment of the United Nations Educational, Scientific and Cultural Organization (UNESCO). The international community sought the need to expound on the vision for scientific and technological progress by including values of dignity, freedom and equality. The idea was that when such values are at the centre of the scientific

[1] Andrea Boggio, 'Freedom of Research and the Right to Science: From Theory to Advocacy', in *The Freedom of Scientific Research: Bridging the Gap between Science and Society* (Manchester University Press 2018) 2 <https://digitalcommons.bryant.edu/cgi/viewcontent.cgi?article=1089&context=histss_jou>.
[2] Lea Shaver, 'The Right to Science: Ensuring That Everyone Benefits from Scientific and Technological Progress' (2015) 4 *European Journal of Human Rights* 416.
[3] ibid 416–417.

research, they are more likely to strengthen rather than challenge the enjoyment of other human rights[4], such as the right of access to healthcare. Stemming from such vision, the right was later adopted in 1966 by the International Covenant on Economic, Social and Cultural Rights (ICESCR). Under Article 15:

> '1. The States Parties to the present Covenant recognize the right of everyone:
>
> (a) To take part in cultural life;
>
> (b) *To enjoy the benefits of scientific progress and its applications*;
>
> (c) To benefit from the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author.
>
> 2. Shall take the steps necessary for the conservation, the development and the diffusion of science and culture.
>
> 3. Undertake to respect the freedom indispensable for scientific research and creative activity.
>
> 4. Recognize the benefits to be derived from the encouragement and development of international contacts and co-operation in the scientific and cultural fields.'

These two provisions address the two main facets of the right to science: the right of individuals to access and enjoy the benefits of scientific advancement and the rights of scientists to freely conduct science and to have the results of their work protected. Although the right to research has been recognised under international law since 1948, it has received little attention from regional and national bodies, human rights activists and scholars.[5] Boggio and Romano aver that the 'right to science' is 'arguably the least known, discussed and enforced international human right.'[6] To borrow from Chalmers et al, the right to science has been overlooked for almost half a century and is now being resuscitated.[7] As a result, the normative content of the right is not clearly set out and there is no consensus on states' duties on this right.[8] Nevertheless, the right to science has risen to the centre of international debates over the past two decades, and progress has been made towards a more comprehensive understanding of this right as will be discussed later in this chapter.

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[4] Lea Shaver, 'The Right to Science: Ensuring That Everyone Benefits from Scientific and Technological Progress' (2015) 4 *European Journal of Human Rights* 417.
[5] Boggio A & Romano CP, 'Freedom of Research and the Right to Science: From Theory to Advocacy', *The Freedom of Scientific Research: Bridging the Gap between Science and Society* (Manchester University Press 2018) <https://digitalcommons.bryant.edu/cgi/viewcontent.cgi?article=1089&context=histss_jou at 5.
[6] ibid 1.
[7] L Chalmers, MB Bracken, B Djulbegovic et al, 'How to Increase Value and Reduce Waste When Research Priorities Are Set' (2014) 383 (9912) *The Lancet* 158.
[8] Lea Shaver, 'The Right to Science and Culture' (2010) 1 *Wisconsin Law Review* 166.

II. THE RIGHT TO SCIENTIFIC RESEARCH

Section 16(1)*(d)* of the South African Constitution stipulates that 'everyone has the right to freedom of expression, which includes … freedom of scientific research.'[9] Similar to all other human rights, this right is not absolute. The government may by virtue of the limitation clause under section 36 of the Constitution limit scientific freedom to prevent the harmful effects of science.[10] The limitation clause provides that rights may be limited 'only in terms of law of general application to the extent that the limitation is reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom.'[11]

In South Africa, the National Health Act (NHA)[12] and its regulations is the key legislation that sets limits on scientific research conducted on humans. Other pieces of legislation may nonetheless also be applicable, depending on the circumstances.[13] For systematic reasons, it will be of great assistance to break down the science of germline gene editing into the different translational stages: basic research, clinical research, and clinical application and to discuss the limitations accordingly.

a) Basic research

Under this section, basic research entails any modifications done to human tissues (gametes, zygotes and embryos) both in vivo and ex vivo. As a starting point, section 57(1) of the NHA prohibits the manipulation of any genetic material including in human gametes, embryos and zygotes for the reproductive cloning of a human being. It also prohibits embryo splitting for similar purposes. As far as the issue of human cloning is concerned, the Act defines it as follows:

> '(a) "reproductive cloning of a human being" means the manipulation of genetic material to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose; and

[9] The Constitution of the Republic of South Africa 1996. Thaldar and Steytler suggest that this right serves the purposes of promoting individual autonomy, facilitating the search for truth, and supporting democracy. See: Thaldar DW, Steytler M 'Time for Cinderella to go to the ball: Reflections on the right to freedom of scientific research' (2021) 138(2) *South African Law Journal* 260–288. https://doi.org/10.47348/SALJ/v138/i2a2.

[10] Yvonne Donders, 'The Right to Enjoy the Benefits of Scientific Progress: In Search of State Obligations in Relation to Health' (2011) 14(4) *Medicine, Health Care and Philosophy* 378.

[11] A Dhai et al 'Ethical and legal controversies in cloning for biomedical research – a South African perspective' (2004) 94(11) *SAMJ* 906–909.

[12] National Health Act 61 of 2003.

[13] The Medicines and Related Substances Control Amendment Act and the Children's Act.

(b) "therapeutic cloning" means the manipulation of genetic material from either adult, zygotic or embryonic cells to alter, for therapeutic purposes, the function of cells or tissues.'[14]

Section 57(6) therefore distinguishes between reproductive and therapeutic cloning. Reproductive cloning entails manipulating genetic material to produce an identical human being whereas therapeutic cloning is the manipulation of genetic material to alter some bodily functions and this includes gene editing. Laurent argues that it is problematic for genetic editing to be placed in the same realm as reproductive cloning under section 57(1) as these are two different practices.[15]

Statutory interpretation generally requires that words be given their ordinary grammatical meaning (literal interpretation). However, it is also a well-known interpretation principle that words in a statute should be construed in their context by allowing for the use of a purposeful approach. Schreiner JA in *Jaga v Dönges; Bhana v Dönges*[16] stated that

'Certainly no less important than the oft repeated statement that the words and, expressions used in a statute must be interpreted according to their ordinary meaning is the statement that they must be interpreted in the light of their context. But it may be useful to stress two points in relation to the application of this principle. The first is that "the context", as here used, is not limited to the language of the rest of the statute regarded as throwing light of a dictionary kind on the part to be interpreted. Often of more importance is the matter of the statute, its apparent scope and purpose, and, within limits, its background. The second point is that the approach to the work of interpreting may be along either of two lines. Either one may split the inquiry into two parts and concentrate, in the first instance, on finding out whether the language to be interpreted has or appears to have one clear ordinary meaning, confining a consideration of the context only to cases where the language appears to admit of more than one meaning; or one may from the beginning consider the context and the language to be interpreted together.'[17]

The dissenting judgment of Schreiner JA in the *Jaga* case was also quoted with approval in *Bato Star Fishing v Minister of Environmental Affairs and Tourism*[18] wherein the Constitutional Court stated that

[14] Ibid s57(6).
[15] Ashleigh Claudia Laurent *A Critical Analysis of the Legality of Future Research and Experimentation of Germ-Line Gene Editing (GGE) in South African Law and Ethics* (an unpublished LLB thesis, University of Pretoria, 2019) 15.
[16] *Jaga v Dönges; Bhana v Dönges* (1950 (4) SA 653 (A)).
[17] ibid 662G–663A.
[18] *Bato Star Fishing (Pty) Ltd v Minister of Environmental Affairs and Tourism* (2004 4 SA 490 (CC)).

> 'the emerging trend in statutory construction is to have regard to the context within which the words occur, even where the words to be construed are clear and unambiguous.'[19]

Accordingly, there is a chance that the term 'reproductive human cloning' could be interpreted literally, leading to a blanket ban on any genetic material engineering that results in the creation of a human being. This argument has been supported by Pillay and Thaldar who aver that the regulatory framework for germline genome editing in South Africa is thought to be ambiguous because the NHA prohibits the reproductive cloning of humans of which its definition of reproductive cloning is broad enough to cover germline genome editing. This peculiar definition compromises the integrity of the law.[20] Townsend and Shozi advance a similar argument by stating that section 57(1), when read in conjunction with section 57(6), strictly prohibits the manipulation of genetic material 'with the aim of obtaining the reproduction of a human being.' According to this interpretation, 'cloning' refers to all methods of manipulating genetic material rather than the connotation typically associated with the word.[21]

However, in giving the provision a purposive interpretation, the mere existence of a distinction between the two types of cloning within the same provision signifies the drafter's intention to distinguish between different types of genetic material alterations that also aim to achieve different results. I am of the view that section 57 (1) of the NHA is drafted with sufficient precision in that although the provision makes mention of genetic manipulation which is a broader term to include activities such as genetic editing, such genetic manipulation is only prohibited if carried out for the reproductive cloning of a human being. Reproductive cloning should be construed to mean the production of genetically identical individuals as has been defined under subsection 6*(a)*. The use of the word 'reproduction' under subsection 6 should be given its dictionary meaning of 'a copy of something'[22] and not its secondary meaning — 'the process of producing new life.'[23] Thus, the type of genetic editing this study is advocating for is not one to reproduce genetically identical human beings but rather altering genetic material to alter the function of certain cells for disease treatment or prevention.

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[19] ibid 91.
[20] S Pillay & DW Thaldar, 'CRISPR: Challenges to South African Biotechnology Law' (2018) 11 *South African Journal of Bioethics and Law* 89, 91.
[21] Beverley Townsend & Bonginkosi Shozi, 'Altering the Human Genome: Mapping the Genome Editing Regulatory System in South Africa' (2021) 24 *Potchefstroom Electronic Law Journal* 1, 8–10.
[22] Cambridge Dictionary pt C1 <https://dictionary.cambridge.org/dictionary/english/reproduction> accessed 4 January 2020.
[23] Cambridge Dictionary pt C2 <https://dictionary.cambridge.org/dictionary/english/reproduction> accessed 4 January 2020.

Regrettably, the terms 'germline' and 'somatic' cells are not expressly defined or distinguished in the NHA regulations. More so, the definition of therapeutic cloning under section 57 mentions a number of human biological components, that is, gametes, zygotic and embryonic stem cells. The majority of gene therapies (somatic editing) use at least one of these human biological components and it is therefore unclear whether the legislature intended to encompass both types of gene editing. Section 57(5) provides that a person who contravenes the provisions of section 57 is guilty of an offence and will on conviction be liable to a fine and/or imprisonment for a period not exceeding five years. It has been argued that the regulatory stance pertaining to human genome editing is somewhat unclear as it is expected that the reader must derive the regulatory stance from the laws and regulations in a fragmented and unsystematic manner.[24] Notwithstanding this, I suggest that this is not necessarily problematic as therapeutic cloning can be argued to encompass germline and somatic editing, none of which have been expressly prohibited.

Furthermore, the Act also prohibits research on stem cells and zygotes older than 14 days. To research zygotes less than 14 days old, researchers must still apply in writing to the Minister while undertaking to document the work for record purposes and should have obtained prior consent from the donor of such stem cells or zygote.[25] Research on embryos within the first 14 days of development is therefore permitted provided the following conditions are met: (a) ministerial consent; (b) donor consent; and (c) a commitment by the researcher to maintain records of the research. If the research advances to the point where it is suited for human clinical trials — for the in-utero transfer of an embryo with an altered genome for reproductive purposes — section 71 of the NHA will be applicable.[26] This will be discussed in the next subsection relating to clinical studies.

Given that research on human germline cells would require human research participants to donate germline cells, it is important to discuss the issue of gamete removal. Now turning to the issue of gamete removal from living persons, section 55 of the NHA stipulates that no person may remove gametes from a living person without the written consent of the person from whom the gametes are removed and such removal should be done in accordance with prescribed conditions. The NHA further specifies that such gametes may only be removed for

[24] Townsend and Shozi op cit note 21 at 155.
[25] National Health Act s 57(4).
[26] Donrich Thaldar and others, 'Human Germline Editing: Legal-Ethical Guidelines for South Africa' (2020) 116 No 9/10 *South African Journal of Science* 2–3.

medical purposes as may be prescribed.[27] In a quest for clarity, the Regulations relating to the use of Human Biological Material (The Regulations)[28] provide more detail on the type of medical purposes gametes may be used for. Regulation 5 states that:

> 'Human biological material, may be removed or withdrawn from living persons for the following medical … purposes –
>
> a) DNA, RNA and chromosome-based genetic testing;
>
> b) *Health research referred to in section 69(3) of the Act*; [emphasis added]
>
> c) Training referred to in section 64(1)(a) of the Act; or (c) Studies of archaeological, medical or heritage value on DNA obtained from human genetic material, conducted in terms of the of the National Heritage Resources Act, 1999 (Act No.25 of 1999).'

Human biological material has been defined to mean 'material from a human being including DNA, RNA, blastomeres, polar bodies, cultured cells, *embryos*, *gametes*, progenitor stem cells, small tissue biopsies and growth factors from the same.'[29] Such removal is to be done by competent persons who by virtue of Regulation 2 may use such gametes for genetic testing, *genetic health research* or therapeutic purposes. However, no person shall carry out genetic health research unless such research has been approved by a registered health research ethics committee referred to in section 73(1) of the NHA.[30]

The regulations use the terms 'genetic testing' and 'genetic health research' at least seven times but for some reason omitted to define them. It is unclear what the intention of the drafters was in making such omission. Thaldar et al aver that human germline editing is likely to be considered as 'genetic health research' given the NHA's broad definition of 'health research' and the fact that germline editing is unquestionably genetic in nature.[31] However, Kirby is of the view that the absence of definitions casts further confusion on South Africa's position regarding germline gene editing.[32] I do not think that is the case as the meanings of 'genetic' and 'testing' are quite clear and hence it should not be confusing that genome editing falls within 'genetic research.' Now turning back to Regulation 5*(c)*, the provision refers to 'health research referred to under section 69(3) of the NHA.' Section 69(3) does not describe any health

[27] National Health Act s56(1).
[28] National Health Act, Regulations relating to the use of human biological material, No. R177 in Government Gazette No. 35099 of 2 March 2012.
[29] National Health Act, Regulations relating to the use of human biological material 2012 reg 1. Emphasis added.
[30] National Health Act, Regulations relating to the use of human biological material 2012 reg 3(2).
[31] Thaldar et al op cit note 26 at 2.
[32] Neil Kirby, 'Gene Editing and South African Law: Medical Law' (2016) 16(3) *Without Prejudice* 16.

research but rather vests the National Health Research Committee with regulating health research carried out by public health authorities. It reads as follows:

> 'The National Health Research Committee must-
>
> (a) determine the health research to be carried out by public health authorities;
>
> (b) ensure that health research agendas and research resources focus on priority health problems
>
> (c) develop and advise the Minister on the application and implementation of an integrated national strategy for health research and
>
> (d) coordinate the research activities of public health authorities.'

However, section 1 of the NHA defines health research as 'any research which contributes to knowledge of … the causes of disease, … the development or new application of pharmaceuticals, medicines and *the development of new applications of health technology*.' I submit that although section 69 may on the face of it appear to be of little or no assistance, it prioritises health research — including genetic health research — that focuses on priority health problems. In the same way, the regulations[33] instruct authorised institutions that perform genetic research or *generate* embryonic stem cells to have separate registers to record such genetic research or *generation of embryonic stem cell lines*. In interpreting the two provisions harmoniously, I submit that the NHA could be interpreted to permit the creation of embryos for genetic health research purposes for reasons substantiated below.

The Cambridge Dictionary meaning of the word 'generate' is to create or cause to exist.[34] I suggest that regulation 12 should be broadly interpreted to mean that researchers are permitted to remove human biological material — gametes — by virtue of Regulation 5 to *create* embryonic stem cells for health research purposes. Should the drafters have intended to limit the generation of such embryonic stem cells from excess IVF embryos, they would have made it clear. What is not expressly forbidden is permissible, and therefore, unless the creation of embryos for research purposes is expressly prohibited, it may be argued to be permissible. In addition, the Regulations permit the removal of gametes for genetic health research. The WHO defines genetic health research to encompass research in the following areas: genetic testing,

[33] National Health Act, Regulations Relating to the Use of Human Biological Material 2012 reg 12.
[34] Cambridge Dictionary <https://dictionary.cambridge.org/dictionary/english/generate> accessed 4 January 2020.

gene therapy, reproductive genomics, genetic databanks and pharmacogenomics.[35] For purposes of this study, pharmacogenomics[36] will therefore include research using CRISPR-CasX to develop optimal TB drugs that focuses on the particular patients' genotype to ensure maximum efficiency.

The overall analysis is that the prohibitions or restrictions under the Act and its regulations are tainted with ambiguity thus making the regulatory regime for germline gene editing in South Africa blurred.[37] The greatest uncertainty is concerning reproductive cloning and the issue of gamete removal in persons. The Regulations relating to the use of Human Biological Material do not provide precise medical procedures under which that gametes may be used. The section however uses a broad term —health research. In a country that is heavily burdened with diseases such as TB, human genome editing may yield valuable results in the prevention of TB. In concluding I wish to summarise my interpretation of the Act and regulations once more. I suggest that genetic editing is only prohibited under the Act only if it is done to reproduce genetically identical human beings. Furthermore, the regulations allow the use of gametes for genetic health research or therapeutic purposes, which I suggest includes human genome editing, therefore prohibiting the creation of research embryos for genetic health research (germline editing) would be a violation of the fundamental freedom of scientific research.

b) Clinical studies

Clinical studies on germline gene editing involve using a living human being as a subject of a study as opposed to the use of human tissue. Given the above, section 12 (2)*(c)* of the Constitution provides that 'everyone has the right to bodily and psychological integrity, which includes the right … not to be subjected to medical or scientific experiments without their informed consent.' In South Africa, research with human subjects is permissible under section 71 of the NHA.

The relevant provision reads as follows:

'(1) … research or experimentation on a living person may only be conducted-

…

[35] World Health Organization, 'Human Genetics Programme' <https://www.who.int/genomics/research/en/> accessed 3 January 2020.
[36] *Pharmacogenomics* focuses on how one's genes affect their response to certain drugs.
[37] Pillay and Thaldar op cit note 20 at 91.

(b) with the written consent of the person after he or she has been informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health.

(2) Where research or experimentation is to be conducted on a minor for a therapeutic purpose, the research or experimentation may only be conducted-

(a) if it is in the best interests of the minor;

…

(c) with the consent of the parent or guardian of the child; and

(d) if the minor is capable of understanding, with the consent of the minor.

(3) (a) Where research or experimentation is to be conducted on a minor for a non-therapeutic purpose, the research or experimentation may only be conducted-

…

(ii) with the consent of the Minister

(iii) with the consent of the parent or guardian of the minor; and

(iv) if the minor is capable of understanding, the consent of the minor.

(b) The Minister may not give consent in circumstances where-

(i) the objects of the research or experimentation can also be achieved if it is conducted on an adult;

(ii) the research or experimentation is not likely to significantly improve scientific understanding of the minor's condition, disease or disorder to such an extent that it will result in significant benefit to the minor or other minors;

(iii) the reasons for the consent to the research or experimentation by the parent or guardian and, if applicable, the minor are contrary to public policy;

(iv) the research or experimentation poses a significant risk to the health of the minor; or

(v) there is some risk to the health or wellbeing of the minor and the potential benefit of the research or experimentation does not significantly outweigh that risk.'

The provision addresses issues of informed consent when performing medical experiments on living persons. It is worth noting that even though the editing occurs on a germline cell before the prospective child is born, the research carries on throughout pregnancy and the child's life.[38] Historically, minors have been pharmaceutical orphans. That is, it has been difficult to implore children in clinical trials due to ethical reasons. This creates a problem for gene editing clinical trials as adults and children are biologically different. Children's anatomy, physiology, and pathology changes significantly on a biological level.[39] Due to their small size, immature

[38] Thaldar et al op cit note 26 at 3.

[39] Vic Larcher, 'Children Are Not Small Adults: Significance of Biological and Cognitive Development in Medical Practice' [2015] *Handbook of the Philosophy of Medicine* 1, 1–3.

anatomy, physiology, and unique pharmacodynamics, infants and very young children exhibit a greater susceptibility to different harms. Organ development and differing metabolisms also determines the patterns of childhood disease, as well as the responses to medicinal therapies.[40] There is need to therefore have clinical trials that are diverse in age and population group to allow pharmaceuticals to develop the paediatric side of CRISPR therapies timeously.

Although the prospective child cannot consent, one vulnerable group that is addressed by section 71 is that of minors. The provision provides that the research may only be conducted on minors if it is in the best interests of the child and with the necessary parental consent. It also provides the requirement of mandatory parental consent for all health research and consent from the Minister of Health for all 'non-therapeutic' research regardless of risk level. This covers genome edits that do not offer the potential of a direct benefit to the child but does offer the prospect of generalised medical or genetic knowledge.[41]

Although section 71 allows adults to freely consent to medical experiments, provided they have been informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health, it is also important to discuss the participation of women of reproductive potential, particularly pregnant and lactating women. If we are to use germline editing to achieve herd immunity against TB, this is the population group we need to prioritise on. Despite the global need for the use of CRISPR therapies during pregnancy, the medical community could lack robust evidence on the safety of the treatment not only on the pregnant woman, but also the developing foetus. There is therefore a possibility of hesitancy of pregnant women as well as lactating women to participate in the clinical trials due to uncertainty on the ways in which the medication will behave in the pregnant body as well as concerns of drug transfer during lactation. This is warranted given the biological differences between pregnant/lactating women and the rest of the population. Accordingly, owing to the discussion under basic research, and the protectionism kind of approach towards children and pregnant women, it is uncertain whether any gene editing clinical studies will ever be this inclusive in South Africa.

[40] ibid.
[41] Thaldar et al op cit note 26 at 3.

c) Clinical application

While gene-editing technology offers benefits that could eventually improve overall health of the people, including providing immunity against TB, its practical application may be far from possible due to the factors discussed above. In addition, owing to the current uncertainty around gene editing, it could be argued that the right to enjoy the benefits of scientific progress and its applications resulting from human genomic research is currently being limited as a way of protecting society from the potential irreversible risk of harm that germline gene editing presents. However, advocating for a positive duty on the government to allow people to profit from gene-editing technology will not be futile at this time. A positive duty trumps whatever is in the NHA – the duty is a Constitutional duty that overrides legislation.

Nevertheless, this only addresses a fraction of the broader question. What justifications exist to limit basic scientific research on human embryos? All the limitations to research with gametes and embryos as already discussed will have to stand the test of the limitation clause as enunciated. Although Dhai et al argue that it is challenging to prove that the restrictions contained in the NHA are unreasonable due to the differing legal positions in other jurisdictions,[42] Although Dhai et al argue that proving that the restrictions contained in the NHA are unreasonable is challenging due to differing legal positions in other jurisdictions, it remains crucial that the relevant provisions of the NHA be assessed using the principles of legality and proportionality.

(i) Condition of legality

One of the conditions set out in section 36 of the Constitution is that the limitation must be determined by law, that is; it must have a basis in legislation. Boggio and Knoppers substantiate this principle by suggesting that the relevant domestic law must be formulated with sufficient precision.[43] Upon analysis of the NHA and its regulations, an inference can be drawn that the provisions are tainted with vagueness. For instance, the regulations do not clearly define the situations under which human biological material (gametes) may be removed. This vagueness is problematic, particularly because section 57(5) of the NHA criminalises certain activities associated with the manipulation of human genetic material. Similarly, persons who violate the regulations are liable to imprisonment of not more than ten years and/or a fine.[44] Given the risk

[42] Dhai and others 'Ethical and legal controversies in cloning for biomedical research – a South African perspective' (2004) 94(11) *SAMJ* 908.
[43] Andrea Boggio, Bartha M Knoppers, Jessica Almqvist et al, 'The Human Right to Science and the Regulation of Human Germline Engineering' (2019) 2 *CRISPR Journal* 14.
[44] National Health Act, Regulations Relating to the Use of Human Biological Material 2012 reg 14.

of facing a criminal charge, which also has reputational costs, scientists are unlikely to undertake other forms of research due to the lingering ambiguities thus stifling innovative research. Vagueness in law can take many various forms and have a variety of effects. One classification of vagueness is vagueness in the content of the law. Similarly, in understanding legal content, there are two distinct ways that ambiguity may also develop. The first and most obvious reason why a law could be vague is if the authoritative text employed by legislators contains vague terms. In such cases, the authoritative text will be open to interpretation and such interpretation often arises in legal proceedings. The second way in which ambiguity of legal content can occur is by conflicts created by various legislations or sections of a piece of legislation, taken in conjunction with facts of a given case.[45] In this case, vagueness in terms of section 57 relates to the first instance — the provision contains vague terms. Christie avers that men may use language to attain more sophisticated forms of social control, and as such vagueness is not always a disadvantage. Using ambiguous language in legal directives, for instance, can delay making ultimate decisions. As such the Legislator may employ ambiguous language to convey their intentions but may be unsure of the precise behaviour they want to forbid.[46] This could be the case with section 57 regarding situations under which human biological material may be removed or the legality of human genome editing in its entirety.

(ii) Proportionality

All limitations under section 36 must be proportional to the goal they seek to achieve. This entails that the limitations imposed must be an outcome of a careful balancing of interests exercise and must be the least intrusive measure that could be used to achieve the desired result.[47] The importance of scientific freedom cannot be down-played. Jordaan notes that 'the right to freedom of scientific research is the lifeblood of scientific progress and the *conditio sine qua non* for the continued improvement of the human condition.'[48] As per Edwin Conklin's famous quote '[T]he increase and diffusion of knowledge depends entirely upon

[45] S Soames, 'What Vagueness and Inconsistency Tell Us about Interpretation', *The Philosophical Foundations of Language in the Law* (Oxford: Oxford University Pres).
[46] George C Christie, 'Vagueness and Legal Language' 48 *Minnesota Law Review* 885, 889–890.
[47] Andrea Boggio, Bartha M Knoppers, Jessica Almqvist et al, 'The Human Right to Science and the Regulation of Human Germline Engineering' (2019) 2 *The CRISPR Journal* 16.
[48] DW Jordaan, 'Science versus Anti–Science: The Law on Pre–Embryo Experimentation' (2007) 124(3) *SALJ* 618.

freedom to search, experiment, criticise and proclaim. Without these freedoms there can be no science.'[49]

I suggest that the limited scope on the types of health research permitted deprives scientists of an essential tool of advancing research on the treatment of TB in humans using CRISPR-CasX. Considering the rate at which the technology is advancing, the restrictions under the NHA and its regulations need to be revisited. It is clear that the law is struggling to match the pace of scientific and technological advances.[50] It would be important to inquire into the legitimacy of the restrictions placed on health research, or more precisely, into the legitimacy of the government's purpose in taking it. This is a low bar to pass as it is rare for a government measure to have no legitimate purpose and few restrictions are struck down at this stage. The legislator should be able to justify the measure as a means to pursue ends for which it is responsible such as preventing irresponsible science.

Next, it is prudent to assess whether the challenged measure is a 'appropriate' means to the achievement of its purpose. A measure just needs to contribute in some way to the legitimate aim to be considered appropriate. It is not necessary for it to be the best or most appropriate solution. If the legislator can credibly prove that the restrictions as contained under the NHA safeguard responsible science, it will pass this test. From this point on, proportionality review of the measures becomes important. This proportionality analysis is frequently operationalized as a least-restrictive means test, which asks whether the legislator's goal may be served with less restrictive alternatives. If the response is affirmative that the legislator's means implored were disproportionate, then it becomes unlawful. This also poses a question of whether these restrictions are truly justifiable in an open and democratic society considering that they were adopted before CRISPR's increased precision in gene editing, thus negating the issue of potential harms that may be caused by the technology.

The restrictions tainted with ambiguity cannot be said to promote the values of an open and democratic society such as human dignity. Scientific freedom can only be said to be fully respected when scientists can freely create and experiment on embryos. Limiting embryo research to IVF supernumerary embryos is not good enough due to the limited number of

[49] Edwin G Conklin, '"Science and Ethics", Address of the Retiring President of the American Association for the Advancement of Science' 86(2244) *Science* 601.
[50] Michael S Pepper, 'Partial Relief from the Regulatory Vacuum Involving Human Tissues through Enactment of Chapter 8 of the National Health Act and Regulations Thereto' (2012) 102(9) *South African Medical Journal* 736.

embryos available.[51] Also, a considerable percentage of those embryos are either not viable or affected by various disorders, affecting the quality of the research output.[52]

One should also bear in mind that the provisions of the NHA were drafted long before genome editing technologies, and thus it is clear that it was not drafted with the application of genomic technology in mind. To do so would be to ostensibly cast the intention of the legislators very wide. To win the fight against TB, we need to ask ourselves what kind of scientific progress needs to be promoted to make the most impact. This calls for the government not to be complacent to the conventional TB treatment methods which have proven to be less suited to other South African populations. Sufficient attention must be given to the choices made in the direction of scientific progress. It is possible that the South African Health Products Regulatory Authority (SAHPRA) may call on applications of germline editing to be registered if germline editing clinical applications are conceivable to fall within the regulatory ambit of the Medicines and Related Substances Control Act (MRSCA). Clinical trial data will be used by SAHPRA to evaluate registration based on its safety, effectiveness, and quality.[53] However, for a germline editing application to be subject to the MRSCA's regulatory authority, it must meet the criteria for either a 'medicine' or a 'medical device'. Section 1 of the MRSCA defines the terms as follows

> ' "medicine" means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in - (a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or (b) restoring, correcting or modifying any somatic or psychic or organic function in man.
>
> "medical device" means any instrument, appliance, material, machine, apparatus, implant or diagnostic reagent - (a) used or purporting to be suitable for use or manufactured or sold for use in - (i) the diagnosis, treatment, mitigation, modification, monitoring or prevention of disease, abnormal physical or mental states or the symptoms thereof; or (ii) restoring, correcting or modifying any somatic or psychic or organic function; or (iii) the diagnosis or prevention of pregnancy, and which does not achieve its purpose through chemical,

[51] National Health Act, Regulations relating to the use of human biological material 2012 reg 7.
[52] Farzaneh Fesahat and others, 'Frequency of Chromosomal Aneuploidy in High Quality Embryos from Young Couples Using Preimplantation Genetic Screening' (2017) 15(5) *International Journal of Reproductive BioMedicine* 297, 302.
[53] Thaldar et al op cit note 26 at 3.

> pharmacological, immunological or metabolic means in or on the human body but which may be assisted in its function by such means…'[54]

Simply put 'a medicine is a *substance* that is used for a medical purpose in humans, while a medical device is an *instrument* that is used for a medical purpose, but that does not achieve its primary intended action by pharmacological, immunological or metabolic means in the human body.'[55] Biological elements employed in genome editing, such as guide RNA, enzymes, and viral vectors qualify as substances given that the court in *Reitzer Pharmaceuticals (Pty) Ltd* v *Registrar of Medicines*[56] determined that a bacterium qualifies as a substance. In this case, the applicant, a pharmaceutical company sought an order referring to the question of whether the definition of medicine according to MRSCA was in conflict with provisions of the Constitution. The applicant's attack on the definition was directed to the word 'used' which could mean anything to treat or cure a disease. The applicant argued that 'even water may be used for restoring, correcting or modifying any somatic or organic function in man namely to quench thirst…'[57] In deciding the matter, the interests of the public represented by the MRSCA were highly influential of the court's decision not to grant an interdict and to tolerate such an extensively broad definition of medicine.

It is therefore not implausible that biological tools like CRISPR-CasX and the viral vectors used to deliver it to target cells could be considered medical devices since they can be considered biological instruments for precision work. Given that germline editing is mostly carried out on human germline cells ex vivo rather than in human organisms, it is unclear whether germline editing applications would be considered to be anything used *in humans*. Thaldar et al argue that while some potential therapeutic uses for human germline modification may be done for medical reasons, other applications will not — for instance, enhancing a person's IQ — therefore falling outside the regulatory scope of the MRSCA.[58] Since the primary aim of this study is to advocate for the use of germline editing for the prevention of TB, such application will qualify as a medical purpose. Furthermore, as discussed in chapter 1, with advanced research, CRISPR CasX could be delivered *in vivo* and *in utero* as opposed to *in vitro* thus qualifying as something that is used *in humans* thus falling within the regulatory

[54] Medicines and Related Substances Control Act, Act 101 of 1965.
[55] Thaldar et al op cit note 26 at 3.
[56] *Reitzer Pharmaceuticals (Pty) Ltd v Registrar of Medicines* 1998 (4) SA 660 (T).
[57] ibid para 683 E-F.
[58] Thaldar et al op cit note 26 at 3.

scope of the MRSCA. Against this background, the relationship between the right of access to healthcare and the right to benefit from scientific progress will be discussed in the next section.

III. THE RIGHT TO ENJOY THE BENEFITS OF SCIENTIFIC PROGRESS AND ITS APPLICATIONS

In human rights discourse, the right to enjoy the benefits of scientific progress has been somewhat unclear and unexplored.[59] Notwithstanding its current status, the existence of the right to benefit from scientific progress is potentially valuable in mitigating the TB epidemic in South Africa by facilitating access to existing novel technologies such as CRISPR. Given that the discovery of new TB treatment methods is based on scientific research, exploring the right to enjoy the benefits of scientific progress — aiding access to recent scientific discoveries — could spur the development of new TB methods that do not exist in the current drug pipeline.

One starting point for conceptualising this right is to understand what enjoying the benefits of its applications entails. Like all rights, the right to the benefits of scientific progress and its applications places on individuals or society at large a particular set of entitlements. As will be conceptualised in this section, the right to enjoy the benefits of scientific progress and its applications has three facets:

- A right of access to beneficial scientific developments;
- A right to be protected from undue interference by the state or third parties in the enjoyment of the right
- A right to be protected from possible harmful effects of scientific and technological development, on both individual and collective levels.

A right of access as a bare minimum entails the ability and opportunity for everyone to benefit from scientific progress without discrimination. Scientific knowledge is a global treasure that should be shared. In the healthcare arena, without the right to benefit from scientific progress, the rest of the society is denied the benefit of early warning, documentation of emerging problems, and access to new disease treatment methods.[60] Therefore, the apparent

[59] Leslie London, Helen Cox & Fons Coomans, 'Multidrug-Resistant TB: Implementing the Right to Health through the Right to Enjoy the Benefits of Scientific Progress' (2016) 18(1) *Health and Human Rights Journal* 26.

[60] Tee L Guidotti, 'Scientific Freedom and Human Rights' (2018) 73(1) *Archives of Environmental & Occupational Health* 2.

benefits of scientific research, such as TB prevention through genome editing, are by right available to society and should be accessible to the individual to the maximum extent possible. While the right to benefit from scientific progress does not entitle an individual to demand the development of new TB treatment drugs, it provides entitlements for the dissemination of scientific discoveries that may be useful in producing innovative TB treatment methods.[61] At the same time, although the second facet requires the state not to unreasonably interfere in science, on the basis of the third facet, the state should interfere where science poses to be harmful to society.

However, it is an ineffectual exercise to promote scientific research particularly when society is not guaranteed the right to benefit from such scientific progress and its applications. Although included in the UDHR and the ICESCR, the South African Constitution does not explicitly recognise the right to enjoy the benefits of scientific progress despite having ratified international instruments such as the ICESCR which do. By ratifying the ICESCR, South Africa is bound by the obligations, goals and standards of the ICESCR and is bound in international law to act in such a way that it does not impinge on the spirit of the ICESCR.[62] How, then, can the right to benefit from scientific progress be enforced in South Africa?

As discussed earlier in this section, the right to benefit from scientific progress does not stand alone, it is reciprocal with other rights, such as the right to take part in cultural life,[63] right to dignity,[64] freedom of expression — freedom to receive or impart information or ideas,[65]— and the right of access to healthcare.[66] In terms of the right of access to healthcare, it is unfeasible for the government to achieve the progressive realization of this right in the absence of having access to progressive medical scientific knowledge such as new preventative methods.

Hence, I suggest that the right to participate in a cultural life of one's choice offers fertile ground for judicial experimentation to incorporate the right to benefit from scientific progress in our law. Section 30 of the Constitution states that 'everyone has the right to participate in

[61] London, Cox and Coomans op cit note 59 at 26–38.
[62] Demichelle Petherbridge, 'South Africa's Pending Ratification of the International Covenant on Economic, Social and Cultural Rights: What Are the Implications?' 1 <http://blogs.sun.ac.za/seraj/files/2012/11/South-Africas-pending-ratification-of-the-ICESCR.pdf> accessed 2 January 2020.
[63] The Constitution of the Republic of South Africa s 30.
[64] Ibid s10.
[65] Ibid s16 (1)*(b)*.
[66] Guidotti op cit note 60 at 4.

the cultural life of their choice.'[67] Although the Constitution is silent on the meaning of cultural life, guidance may be sought from relevant case law from South Africa on section 30 of the Constitution and how scholars have interpreted the right to take part in cultural life as enumerated in Article 15(1)*(a)* of the ICESCR and Article 27 of the UDHR. According to the UNESCO Mexico City Declaration on Cultural Policies World Conference on Cultural Policies:

> '… in its widest sense, culture may now be said to be the whole complex of distinctive spiritual, material, *intellectual* and emotional features that *characterize a society or social group*. It includes not only the arts and letters, but also modes of life, the fundamental rights of the human being, value systems, traditions and beliefs.'[68]

In further considering the meaning of culture, O'Regan J in *MEC for Education, KwaZulu-Natal v Pillay*[69] stated that

> 'My understanding of how our Constitution requires us to approach the rights to culture, therefore, emphasises four things: *cultural rights are associative practices*, which are protected because of the meaning that shared practices give to individuals and *to succeed in a claim relating to a cultural practice a litigant will need to establish its associative quality*; an approach to cultural rights in our Constitution must be based on the value of human dignity which means that we value cultural practices because they afford individuals the possibility and choice to live a meaningful life; cultural rights are protected in our Constitution in the light of a clear constitutional purpose to establish unity and solidarity amongst all who live in our diverse society . . . .'[70]

As is apparent from both definitions, 'culture' becomes a metonym for any social group that shares similar intellectual, spiritual, emotional or material values. Culture therefore should not be narrowly given its anthropological meaning of traditional practices but should be broadly interpreted to include areas of intellectual discoveries in the sciences.[71] Currie defines culture as 'the practice of intellectual and artistic activity and the works that result from that activity.'[72] The scientific community shares similar intellectual values and interests and scientific research

[67] The Constitution of the Republic of South Africa.
[68] UNESCO, 'Mexico City Declaration on Cultural Policies World Conference on Cultural Policies' <https://culturalrights net/descargas/drets_culturals401.pdf> accessed 3 January 2020. Emphases added.
[69] *MEC for Education, KwaZuluNatal v Pillay* (2008 (1) SA 474 (CC)).
[70] ibid 157.
[71] Shaver op cit note 4 at 156.
[72] Iain Currie, 'Minority Rights: Education, Culture, and Language', *Constitutional Law of South Africa* (Juta Kenwyn) 35.19.

in general is their culture. According to the Constitution, 'persons belonging to a cultural community may not be denied the right, with other members of that community — (a) to enjoy their culture … and (b) to form, join and maintain cultural…associations…'[73]

The concept of culture referred to in sections 30 and 31 of the Constitution, according to O'Regan J is the anthropological conception of culture which refers to the way of life of a particular community, and the rights in those provisions are associative rights exercised by individual human beings that bolster the existence of cultural, religious, and linguistic groups so long as individuals remain committed to living their lives in that form of association.[74] It is apparent that Section 31 must be construed in light of Section 30, which grants the right to belong to a certain culture. Section 30 guarantees cultural liberty whereas section 31 protects the practice of one's culture rather than belonging to the culture itself. Maintaining cultural associations then touches on the freedom of expression. The Mexico City Declaration even succinctly states that 'freedom of expression is essential for the creative activities of artists and intellectuals alike.'[75] Members of such culture have 'the right to freedom of expression, which includes — freedom to receive or impart information or ideas … and freedom of scientific research.'[76] Using this analogy, the right to benefit from the scientific progress falls within the ambit of the freedom to receive or impart ideas.

This freedom should be construed to include the society at large. General Comment No 21[77] on the right of everyone to take part in cultural life has expounded on its normative content. According to the UN Committee on Economic, Social and Cultural Rights (CESCR), for purposes of implementing article 15 (1) (a), culture encompasses, *inter alia*:

> '… methods of production or technology… through which individuals, groups of individuals and communities express their humanity and the meaning they give to their existence and build their world view representing their encounter with the external forces affecting their lives.'[78]

More so, the committee elucidates on the meaning of 'to take part in or to participate in cultural life.' General comment no 21 provides that this falls into three distinct components: (a)

[73] The Constitution of the Republic of South Africa ss 31 (1)*(a) – (b)*.
[74] *MEC for Education, KwaZulu-Natal v Pillay* op cit note 69 at para 150.
[75] UNESCO op cit note 68 at para 27.
[76] The Constitution of the Republic of South Africa s 16 (1).
[77] 'General Comment No. 21, Right of Everyone to Take Part in Cultural Life (Art. 15, Para. 1*(a)*, of the International Covenant on Economic, Social and Cultural Rights)' <https://www refworld.org/docid/4ed35bae2 html> accessed 3 January 2020.
[78] ibid 13.

participation in, (b) access to, and (c) contribution to cultural life. Participation must be loosely construed to mean the freedom to choose whether to identify with a particular community, while 'access to' covers 'the right of everyone — alone, in association with others or as a community — to know and understand his or her own culture *and that of others through education and information*.[79]

Should society have the right to learn about the culture of others — in this instance, how scientists have used CRISPR-Cas9 to formulate effective prevention against TB — what then should stop them from benefiting from such information owing to the fact that 'everyone has the right to any information that is held by another person and that is required for the exercise or protection of any rights.'[80] It is undisputed that South Africans are in dire need of scientific knowledge that will notably improve the standards of healthcare in the country. Only when South Africans are enlightened to the alternative forms of treatment can they demand what is best suited for them from the government. Paragraph 12 of General Comment no 14 clarifies that accommodation and quality are some of the vital legally enforceable components in the right to health.[81] Plaks and Butler define accommodation to mean that the healthcare facilities provided by the government must meet the patient's needs and should be to the patient's satisfaction.[82]

As already noted above, it is a Constitutional imperative that everyone has their dignity respected and protected.[83]Although it is difficult to define dignity in precise terms, one of the precepts of human dignity has to do with the defence of personality rights such as self-worth and reputation.[84] All too often people suffering from TB find dignity absent in their dealings with healthcare providers and with society as a whole. They feel demeaned by how they are treated.[85] Having said so, society must benefit from scientific progress made in the treatment of TB as a matter of protecting their human dignity. Incorporating the aspect dignity in advocating for the right to benefit from scientific progress is fundamental to dealing away with

[79] Ibid ss15 *(a)* – *(b)*. Emphasis added.
[80] The Constitution of the Republic of South Africa s 31(1)*(b)*.
[81] 'General Comment No. 14, E/C.12/2000/4 (2000)' <https://tbinternet.ohchr.org/_layouts/15/treatybodyexternal/Download.aspx?symbolno=E%2fC.12%2f2000%2f4&Lang=en> accessed 16 July 2019.
[82] S Plaks and MBJ Butler, 'Access to Public Healthcare in South Africa' (2012) 12 *South African Actuarial Journal* 131–149.
[83] The Constitution of the Republic of South Africa s 10.
[84] Donrich W Jordaan *Medical Biotechnology Law in South Africa: A Human Rights Analysis of Selected Topics* (published PhD thesis, University of Cape Town, 2012) 22.
[85] Amy Green, 'Incurable TB: Patients Die without Dignity' *Health E-News* (24 March 2017) <https://health-e.org.za/2017/03/24/incurable-tb-patients-die-without-dignity/> accessed 15 January 2020.

such stigma and discrimination. There is nothing dignified about subjecting people to years of suffering from multi-drug resistant TB when the TB could have been prevented.

In the field of biological sciences, the right to scientific research is often balanced with the concept of human dignity.[86] If the right to scientific research can be limited in certain instances on the basis of the need to protect human dignity, to the contrary, restricting the dissemination of scientific knowledge that has the potential to improve healthcare standards equally tramples on human dignity. Human dignity is equally as important in regulating scientific research as scientific research is in upholding human dignity.

In summary, while the right to benefit from scientific progress allows a greater fulfilment of other rights, such as the right of access to healthcare, the absence of specific provisions in our Constitution to protect this right requires that this freedom be defended as a specific aspect of the broader freedoms.

IV. TO WHAT EXTENT WILL HUMAN GENOME EDITING BE PERMITTED IN TRANSLATIONAL AND CLINICAL MEDICINE*?*

CRISPR's potential for developing treatments in humans seems nearly endless. However, the anticipation for the future use of CRISPR therapies is followed by concerns as to how and to what degree human genome editing will be permitted. While issues surrounding the risks presented by human genome editing are at the forefront of this debate, a detailed discussion on risk assessment follows in the next chapter. This section focuses on the translational pathway to the clinical use of gene-editing technology and the possible timeline on its use for the prevention or treatment of TB.

In 2020, the International Commission on the Clinical Use of Human Germline Genome Editing[87] released a report with the aim of 'defining a responsible pathway for clinical use of heritable human genome editing (HHGE)'. The report suggests six categories of potential uses of HHGE:

> '(A) cases in which all of the prospective parents' children would inherit the disease causing

[86] Amedeo Santosuosso, Valentina Sellaroli & Elisabetta Fabio, 'What Constitutional Protection for Freedom of Scientific Research?' (2007) 33 *J Med Ethics* 343.
[87] National Academy of Sciences, 'Heritable Human Genome Editing' (2020) <https://doi.org/10.17226/25665.>.

genotype for a serious monogenic disease (defined in this report as a monogenic disease that causes severe morbidity or premature death);

(B) cases in which some but not all of the prospective parents' children would inherit the pathogenic genotype for a serious monogenic disease;

(C) cases involving other monogenic conditions with less serious impact;

(D) cases involving polygenic diseases;

(E) cases involving other applications of HHGE, including changes that would enhance or introduce new traits or attempt to eliminate certain diseases from the human population; and

(F) the special circumstance of monogenic conditions that cause infertility.'

The Commission, under Recommendation 4,[88] suggests that 'initial uses of heritable human genome editing, should a country decide to permit them, should be limited to serious monogenic diseases.' Based on Recommendation 4, it is clear that the Commission considers that only applications in Category A and some in Category B above should qualify for the initial uses of HHGE. It may seem logical that initial applications of HHGE should be reserved for serious monogenic disease as editing a gene variant associated with such a polygenic disease will typically have little effect on risk of the disease. In other words, preventing the disease might require more different edits, some of which could produce adverse effects because of other biological roles that the gene might play. However, the report is unclear on how soon other applications of HHGE will become more compelling. This raises great public health unease as most 'serious' monogenic diseases are rare and usually not severely life-threatening. Instead, polygenic diseases such as hypertension and diabetes are more common and causing a great burden on most healthcare systems, including South Africa's.

Again, Recommendation 4 suggests that the initial uses of HHGE should be limited 'to situations in which prospective parents have no option for having a genetically-related child that does not have the serious monogenic disease …' Similarly, in 2020, the Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing released for comment a Draft Governance Framework on Human Genome Editing.[89]

[88] ibid 9.

[89] Its aim is to 'advise and make recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing.' See 'WHO Expert Advisory Committee on Developing

The Draft Framework equally suggests that, where possible, people should make use of more acceptable technological alternatives to germline editing such as Preimplantation Genetic Testing – Aneuploidies (PGT-A) and adoption.

These recommendations therefore introduce the debate of whether there is any reasonable reason to pursue human genome editing since technologies such as PGT-A are already being used to select disease-free offspring.[90] PGT enables the genetic examination of in vitro embryos for the existence of genetic disorders.[91] Although PGT has been around since 1990, it is still a very limited service in South Africa.[92] The South African legislative framework lacks strict regulatory policies that govern the use of PGT. Although PGT is not specifically mentioned in the National Health Act (NHA), its content is broad enough to permit the use of PGT for genetic disorders as well as for human leukocyte antigen (HLA) matching[93] for donor sibling. The NHA prohibits removal of embryonic, placental, or fetal tissue, stem cells, and umbilical cord, but not umbilical cord progenitor cells.[94] The NHA Regulations Relating to Artificial Fertilisation of Persons govern the removal of gametes from living individuals and their use in such. Accordingly, it governs the operations of fertility clinics, the removal or withdrawal and storage of gametes, the payment for such removal or withdrawal, the donation of gametes, the management of artificial insemination, the transfer of embryos, the storage of embryos, and the destruction of embryos and zygotes. Prior to the 2012 Regulations, persons were allowed to choose the sex of the embryo(s) to implant.[95] Under the 2012 Regulations, Regulation 13 prohibited preimplantation and prenatal testing done solely for sex selection unless there is a serious sex-related or sex-limited genetic condition.[96] The Health Professions Council of South Africa (HPCSA) Guidelines for Reproductive Health clearly state that PGT should not be used as a means of sex discrimination against either sex (especially the female sex), but may be

Global Standards for Governance and Oversight of Human Genome Editing. Human Genome Editing: A Final Framework for Governance. 2021' <https://www.who.int/publications/i/item/9789240030060> accessed 13 August 2021.

[90] Nancy MP King, 'Human Gene-Editing Research: Is the Future Here Yet?' (2019) 97(5) *North Carolina Law Review* 1074.

[91] S Soni, 'Prêt-à-Porter Procreation: Contemplating the Ban on Preimplantation Sex Selection' (2019) 22 *Potchefstroom Electronic Law Journal* 1, 1–3.

[92] Bianca Carzis and others, 'Review of 10 Years of Preimplantation Genetic Diagnosis in South Africa: Implications for a Low-to-Middle-Income Country' (2019) 36(9) *Journal of Assisted Reproduction and Genetics* 1909.

[93] HLA matching is used to match patients and donors for blood or marrow transplants.

[94] National Health Act s 56(2)(a)(iv).

[95] Soni op cit note 91 at 16.

[96] Regulations Relating to Artificial Fertilisation of Persons 2012.

utilized if the healthcare professional deems it necessary to prevent a sex-linked genetic condition.[97]

In July 2022, the Pretoria High Court in the case of *Surrogacy Advisory Group* v *Minister of Health*[98] overturned the statutory ban on non-medical preimplantation sex selection. The Applicant in this case contested the constitutionality of various regulations made in terms of the National Health Act, including regulation 13 which prohibited preimplantation sex-selection. The Applicant argued that the choice of whether and how to have children can be seen as a component of reproductive autonomy, which encompasses sex selection. Emerging reproductive technologies have increased the number of possibilities thus expanding reproductive freedom or liberties one may have. Accordingly, a right to sex choice would fall under the ambit of reproductive rights.[99] Furthermore, by highlighting the fact that there are many reasons for wanting a child of a particular sex, the Applicant sought to steer the narrative away from sexism. These factors included wanting a companion of a particular sex, feeling more qualified to raise a child of a certain sex, wanting to create a family with the ideal balance of boys and girls, or even for traditional or religious reasons.[100] All of these factors, according to the Applicant, are personal choices that should be protected under the right to privacy.

According to the State, the right to privacy does not give people absolute freedom to act however they like without respect for the rights of others or the public good. The State advanced a number of arguments for opposing sex selection. It was argued that non-medical preimplantation sex selection impacts on the interests of women, unborn children, and the society at large. Among others, sex selection may run counter to the ideas of the concerned healthcare professionals; it may psychologically harm the offspring; and it may even change the population's sex ratio.[101] According to the judgment, although an inherently private act may have other-regarding repercussions, this does not undermine its fundamental nature as being private and such an act includes selecting the sex of one's child.

Given the array of opportunities that reproductive rights open up, the question then becomes, can one's susceptibility to TB be easily identified and remedied through PGT? While very unlikely, pursuing this route would also necessitate that the prospective parents make use

[97] HPCSA Guidelines for Good Practice in the Health Care Professions reg 9.2 & 9.3.
[98] *Surrogacy Advisory Group v Minister of Health* (2022) 4 All SA 187.
[99] ibid para 97.
[100] ibid para 96.
[101] ibid paras 99–108.

of IVF of which most of them are met by a hefty price tag few can afford.[102] The total cost of IVF can range from R120,000 to R300,000 or more because achieving a viable pregnancy usually requires more than one treatment cycle.[103] Only about seventeen per cent of South Africans have private health insurance and only elite medical aid plans cover part of the IVF medical procedure. As such, most persons wanting to make use of the service are forced to pay for the procedure out of pocket. This suggests that pursuing reproductive technologies such as PGT is not a route most South Africans would be willing to take, given their financial circumstances. Therefore, it does not seem prudent to restrict clinical applications of human genome editing to instances where it is not possible to select an unaffected embryo.[104]

The draft recommendations also explore the question of whether prospective parents should show evidence of having used other technologies such as Non-Invasive Prenatal Testing (NIPT), for instance, before pursuing human genome editing. The NIPT is a highly sensitive test that is carried out in the first and second trimester of pregnancy to check for chromosome abnormalities in a foetus.[105] This then tasks us to consider the incidences of vertical transmission of TB and whether NIPT could be a possible solution. Vertical transmission of TB refers to the transplacental transmission of TB through the umbilical veins to the foetus' liver and lungs,[106] and the foetus then develops what is known as Congenital Tuberculosis (CTB). Cases of CTB are considered to be uncommon and mostly misdiagnosed as it displays little or no symptoms in the baby during pregnancy and presents nonspecific symptoms in new-borns.[107] More so, the vertical transmission rate of TB is estimated to be about only sixteen per cent.[108] Differentiating between congenital and early postnatally acquired TB is also difficult.[109] Since there are not many cases of congenital TB, there have not been any developments in therapeutic trials to enhance how it should be diagnosed and treated

[102] Wilma Stassen, 'Cutting the Cost to Conceive' (15 January 2015) <https://health-e.org.za/2015/01/15/cutting-cost-conceive/> accessed 11 January 2021.
[103] See https://capefertility.co.za/about-us/costs-of-treatment/, accessed 2 November 2022.
[104] King op cit note 90 at 1075.
[105] CN Mnyani, E Nicolaou & S Bister, 'The Value and Role of Non-Invasive Prenatal Testing in a Select South African Population' (2016) 106(10) *South African Medical Journal* 1047.
[106] Hema Mittal, Saurabhi Das & MMA Faridi, 'Management of Newborn Infant Born to Mother Suffering from Tuberculosis: Current Recommendations & Gaps in Knowledge' (2014) 140(1) *Indian Journal of Medical Research* 32, 33.
[107] Jui-Ju Yeh, Sheng-Chieh Lin & Wen-Chuan Lin, 'Congenital Tuberculosis in a Neonate: A Case Report and Literature Review' (2019) 7 *Frontiers in Pediatrics* 255–257.
[108] Xiaoling Zhang and others, 'Congenital Tuberculosis after in Vitro Fertilization: Suggestion for Tuberculosis Tests in Infertile Women in Developing Countries' (2018) 46(12) *Journal of International Medical Research* 5316, 5316–5318.
[109] Manou Irmina Saramba & Dongchi Zhao, 'A Perspective of the Diagnosis and Management of Congenital Tuberculosis' [2016] *Journal of Pathogens* 1, 3.

prenatally.[110] As a result, there are no concrete recommendations for treating congenital TB thus rendering the use of NIPT unhelpful. Congenital TB is treated afterbirth similar to postpartum acquired TB.[111]

Even if advances in medical technologies evolve to allow the efficient diagnosis and treatment of congenital TB through the use of CRISPR-TB as illustrated in chapter 1, I suggest that NIPT should not be regarded as less morally problematic as compared to human genome editing. Intrinsically, under NIPT, the differing genetic trait is given such gross negative significance to make all other traits of that (would-be) person insignificant.[112] Hence, it is difficult to conceive how the 'seek and destroy' approach of current NIPT technologies would seem less problematic when compared to human genome editing which is aimed at the repairing heritable disabling genetic traits.

Under Recommendation 6, proposals for clinical use should include plans to evaluate the human embryos coupled with monitoring the resulting pregnancy and long-term follow up of resulting children and adults. Again, the Commission is unclear on the timeline in which this monitoring exercise is to be carried out. Will this be a single generational exercise? Perhaps so. Because the overall impression of the report is that HHGE should proceed incrementally, will other possible applications of HHGE be placed on hold until the first clinical application has been cleared as 'safe'? Even so, will these adults be lifelong research subjects? If in the affirmative, the world will need to wait for at least thirty years for the resulting children — edited for serious monogenic diseases — to become adults before other applications of HGE are permitted.

It is also worrying that the pathogenesis of TB remains poorly understood as there are conflicting studies on whether to classify TB as a monogenic or polygenic disease.[113] In such an unclear case, treatment of TB would fall in either category C or D outlined above, failing which, one may proceed under Category E as an 'attempt to eliminate certain diseases from the human population.' In my view, the Commission's classification of this application in the same category as one of genetic enhancement emphasises the blurry line in drawing a distinction between human genome editing for disease prevention and enhancement as certain preventative

[110] ibid 4.
[111] ibid.
[112] V Parens & A Asch, 'The Disability Rights Critique of Prenatal Testing: Reflections and Recommendations', *Prenatal testing and disability rights* (Georgetown University Press 2000).
[113] A Alcaïs and others, 'Genetic Susceptibility to Tuberculosis: From Monogenic to Polygenic Inheritance' (2001) 4 *Sepsis* 238.

interventions might incidentally have enhancing effects. For instance, in the case of TB prevention, human genome editing will undoubtedly extend the recipient's genetic capabilities beyond the normal range thus being tantamount to enhancement.[114] Juengst et al therefore argue that most clinical applications of germline editing fall within the category of preventative interventions which then opens the door to enhancement concerns.[115] The idea of genetic enhancement is particularly problematic since it involves a quest for dominance over the natural environment and, more importantly, self-mastery.[116] Juengst et al further argue that this necessitates the global community to think more deeply about what 'prevention' should entail in the human genome editing sense and establish appropriate regulatory measures.[117] Buchanan argues that it is irrational to claim that altering one's genome is appropriate when treating disease and dysfunction but not when enhancing regular functioning.[118] He argues that it does not follow that one should never attempt to enhance their own or other people's lives because 'one ought to be appreciative of the good things one has and aware that many of them are unearned.'[119]

However, Sandel argues that by promoting genetic enhancement, our genetic abilities would no longer be seen as gifts for which we are indebted, but rather as achievements for which we are responsible.[120] However, as Kass points out, the problem with such an argument is that in any case we rarely meekly accept the 'giftedness' of illness and dysfunction.[121] Sandel echoes the following:

> 'Although medical treatment intervenes in nature, it does so for the sake of health, and so does not represent a boundless bid for mastery and domination. Even strenuous attempts to treat or cure disease do not constitute a Promethean assault on the given. The reason is that medicine is governed, or at least guided, by the norm of restoring and preserving the natural human functions that constitute health.'[122]

[114] Eric T Juengst and others, 'Is Enhancement the Price of Prevention in Human Gene Editing?' (2018) 1(6) *The CRISPR Journal* 353.
[115] ibid 354.
[116] LR Kass, 'Ageless Bodies, Happy Souls: Biotechnology and the Pursuit of Perfection' (2003) 1 *The New Atlantis* 9, 9–12.
[117] Juengst and others op cit note 114 at 354.
[118] Buchanan (n 149) 3.
[119] ibid 3–5.
[120] M Sandel, *The Case Against Perfection* (The Belknap Press of Harvard University Press 2007) 86–87.
[121] Kass op cit note 116 at 19.
[122] Sandel op cit note 120 at 46–47.

The difference between treating sickness and enhancing function, according to Parens, is that medical treatment either improves or restores normal human functioning.[123] This definition takes into account the dual use nature of medical interventions since most interventions can be used to improve or restore. Harris also argues that illness and disability are a normal part of how people function therefore, to view enhancement as improvement of normal functioning would erase the practice of medicine altogether.[124] For example, under this definition, making use of CRISPR therapies on TB patients would be restorative, whereas doing so for individuals with no known pathology would be considered enhancement. Increasing one's resistance to TB infection in a person of average health and no known susceptibility would not be viewed as curing the disease or even preventing it as it is unlikely to occur, but rather acquiring boosted resistance to TB akin to immunological enhancement. Hence, the WHO Draft Framework clearly states that decisions about the permissibility of human genome editing for enhancement purposes therefore need to take into account this dual-use dilemma.[125]

Although these reports attempt to offer guidance on the translational pathways of gene editing, what is frequently omitted in these reports are the current challenges to basic gene-editing research. If our main aim is to use human genome editing to avoid TB-related deaths, our focus should be on establishing pathways that promote responsible research instead of prematurely identifying clinical pathways. Research involving human embryos has been an ethically fraught problem that has culminated in the imposition of a number of restrictions on embryo research in South Africa. Without promoting the right to scientific research, human genome editing will unlikely take off. This is so because a number of CRISPR research on TB may be abandoned as scientists are forced to negotiate through incredibly convoluted and ambiguous legislation that South Africa has cobbled together over the years of which if in infringement, the scientists will be liable to imprisonment.

Furthermore, the obligation to respect bestows a duty on the government to honour the freedoms and autonomy of the people by not unnecessarily interfering with access to such novel technologies. Accordingly, the permissibility of the clinical translation of CRISPR therapies is a consideration to be made by society as a whole and not one the government can

[123] E Parens, *Enhancing Human Traits: Ethical and Social Implications* (Georgetown University Press 1998) 1–10.
[124] J Harris, *Enhancing Evolution: The Ethical Case for Making Better People* (Princeton University Press 2007) 35.
[125] 'WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. Human Genome Editing: A Final Framework for Governance. 2021' at 11–12.

make alone. Policymakers should consider all these inputs in permitting the clinical translation of gene-editing technology. Although the international community may provide some regulatory framework on the clinical translation of gene edition, South Africa needs to develop its national regulatory framework taking into account its people's preferences and needs, and that can only best be achieved through active public participation which is a Constitutional imperative. This can be achieved through conducting Deliberative Public engagement studies.

Lastly, issues of social justice and non-discrimination are governing principles of the WHO Framework. It states that germline editing 'if approved … raises concerns with regard to fairness, social justice and non-discrimination … .'[126] And so, like many of the questions raised by human genome editing, 'how can the possible negative social effects of germline editing be addressed, including the risk of exacerbating social inequalities if the new technology is not made accessible on an equitable basis?' [127] Thaldar et al aver that the regulation of human genome editing should therefore enhance mechanisms that seek to promote access to the technology.[128]

V. PUBLIC VIEWS ON THE BENEFITS OF AND CONCERNS ABOUT THE USE OF HUMAN HERITABLE GENOME EDITING

As scientific research pushes the boundaries of knowledge, ethical and societal issues are frequently brought up by these new discoveries and technology. Regarding Human Heritable Genome Editing (HHGE), the public's sentiments may range from astonishment to optimism about impending new therapies, perplexity, and outright opposition.[129] Deliberative Public Engagement (DPE) must be properly and thoughtfully carried out, in that is has to be as inclusive as possible to acquire the diverse viewpoints available in a pluralistic society. Otherwise, it runs the risk of omitting significant public questions and concerns or of failing to define the pertinent technology-related issues. DPE is a crucial component in developing policy or regulatory framework, particularly when reviewing contentious issues that involve strongly

[126] ibid 28.
[127] Rumiana Yotova, 'Regulating Genome Editing under International Human Rights Law' (2020) *British Institute of International and Comparative Law* 659.
[128] Donrich Thaldar and others, 'Human Germline Editing: Legal-Ethical Guidelines for South Africa' (2020) 116 *South African Journal of Science* 5.
[129] Ana S Iltis, Sarah Hoover and Kirstin RW Matthews, 'Public and Stakeholder Engagement in Developing Human Heritable Genome Editing Policies: What Does It Mean and What Should It Mean?' [2021] *Frontiers in Political Science* 1, 1.

held moral and religious beliefs and areas where there are a lot of questions or ambiguities, as heritable human genome editing.

A 2021 opinion by the European Group on Ethics emphasized the potential role public engagement in the formulation of HHGE policy. That is, public participation can assist policymakers in deciding where to draw the line on the numerous ethical concerns brought up by HHGE.[130] An analysis of public engagement studies on HHGE reveals that the general public around the world is accepting of at least some therapeutic uses of the technology, such as using HHGE to prevent a child from inheriting a genetic health condition.[131] For instance, in 2017 the Royal Society commissioned a survey wherein 76 per cent of British adults agreed that genome editing should be used to 'correct a disorder so that the correction would also be inherited by any children that person has.'[132] On the other side, little support was found in the Royal Society study to support HHGE in the UK for enhancement. The public generally considered the use of HHGE to edit for enhanced genetic traits as needless and undesirable.[133]

Between October 2019 and March 2020, the PEW Research Centre conducted a study in twenty countries across Europe, Russia, the Americas and the Asia-Pacific region to establish public perceptions on biotechnology and the relationship between science and religion.[134] According to the PEW Research Centre, a median of sixty per cent of respondents in all twenty countries opined that using HHGE to reduce the risk of a serious disease that could occur over the course of the child's lifetime was appropriate. However, significantly fewer respondents (a median of fourteen per cent) felt it was appropriate to use HHGE to boost a prospective child's intelligence.[135] Similarly, according to a survey conducted by the Associated Press-NORC Center for Public Affairs Research (AP-NORC), seventy-one per cent of Americans support

[130] Donrich Thaldar and others, 'A Deliberative Public Engagement Study on Heritable Human Genome Editing among South Africans: Study Results' (2022) 17(11) *PLoS ONE* 1, 2.
[131] ibid 4.
[132] Anita van Mil, Henrietta Hopkins and Suzannah Kinsella, 'Potential Uses for Genetic Technologies: Dialogue and Engagement Research Conducted on Behalf of the Royal Society' (2017) 58 <https://royalsociety.org/~/media/policy/projects/gene-tech/genetic-technologies-public-dialogue-hvm-full-report.pdf> accessed 1 December 2022.
[133] ibid 58–59.
[134] Cary Funk and others, 'Biotechnology Research Viewed with Caution Globally, but Most Support Gene Editing for Babies to Treat Disease' (PEW Research Center 2020) 3 <https://www.pewresearch.org/science/wp-content/uploads/sites/16/2020/12/PS_2020.12.10_international-science-religion_REPORT.pdf> accessed 2 December 2022.
[135] ibid 11.

HHGE as a means of preventing the birth of children with deadly or incurable disorders.[136] It can therefore be discerned that the public is generally tolerant of HHGE applications, if used to avoid the inheritance of genetic health disorders or to prevent serious health conditions from occurring.

In 2021, a deliberative public engagement study on heritable human genome editing was conducted among South Africans.[137] The study was limited to thirty participants but was inclusive in terms of racial, gender, educational, age, and religious/belief demographic metrics.[138] Three themes served as the framework for the study — the use of HHGE for 'preventing the inheritance of genetic health conditions, immunity against developing health conditions, and the enhancement of genetic traits.'[139] The use of HHGE to prevent genetic illnesses issues and immunity against serious diseases was overwhelmingly supported, even those that are largely preventable, provided that such uses of HHGE are demonstrated to be safe and effective. Significant majorities opposed the use of HHGE for enhancement.[140] Interestingly, the DPE did not generalise the use of HHGE for immunity against developing health conditions, but rather there was specific focus on the use of HHGE for immunity to contracting TB, HIV/AIDS and Covid-19. In the cases of TB and HIV/AIDS, HHGE for immunity garnered overwhelmingly positive support, but in the case of Covid-19, that support was less strong.[141] Since this study is premised on the use of HHGE to provide immunity against TB, much attention shall be given on the survey results relating to genome editing for immunity against TB. Proposal 6 (P6) of the DPE study stated that 'provided that it is safe and effective, our country's laws should allow parents to choose to use genome editing before a child's birth to make the child immune to contracting a serious disease like TB during the child's life.' In each proposal, participants had three possible responses: Yes, always; Yes, subject to certain conditions; and No, never. In response to this proposal (P6) almost fifty-nine per cent of participants agreed unconditionally to the use of HHGE for immunity against TB, while thirty-four per cent agreed subject to a few conditions and seven per cent disagreed. TB

[136] 'Human Genetic Engineering' *The Associated Press-NORC Center for Public Affairs Research* (Chicago: NORC, 2018) <https://apnorc.org/projects/human-genetic-engineering/> accessed 1 December 2022.
[137] Ethical clearance was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (protocol reference number HSSREC/00002595/ 2021).
[138] Thaldar et al op cit note 130 at 6.
[139] ibid 7.
[140] ibid 16.
[141] ibid 10.

was therefore considered as sufficiently serious disease to warrant the use of HHGE. This alludes to the severity of the TB epidemic in South Africa and its seriousness to South Africans.

This contrasts with participants from a survey conducted among the Dutch public who characterized such applications of HHGE as immoral or as the start of a slippery slope towards unethical enhancements. Although the Dutch survey focused on HIV/AIDS, TB is considered one of the most prevalent opportunistic infections to affect HIV patients. Thus, public opinions regarding the use of HHGE on HIV/AIDS can to a greater extent be considered as synchronous to their views on acquiring TB immunity. The survey was completed by 1013 participants and only 30.4 per cent of participants agreed to the use of HHGE for HIV resistance and an overwhelming 69.8 per cent were against it. Thirty-one per cent of the participants voted that HHGE would not necessarily improve their child's quality of life while a majority of sixty-three per cent agreed that HHGE is unacceptable as there are alternatives available to obtain the same result.[142] Majority — 74 per cent — of the participants also agreed that HHGE is not an effective treatment but it rather starts a slippery slope towards morally unacceptable applications.[143] In discussing the vast difference between South African and Dutch results, it is important to note that the prevalence of TB in Europe is among the lowest in the world.[144] For instance, the incidence of TB in the Netherlands in 2020 was 4.1 cases per 100,000 individuals and continues to decline,[145] whereas the incidence of TB in South Africa was 520 cases per 100,000 individuals.[146] It is therefore evident that in countries where TB and HIV/Aids are not epidemics as in South Africa, public opinions on the use of HHGE for immunity against TB are likely to be different. Thaldar et al argue that these findings support the claims made by academics that the binary of therapy versus enhancement is a problematic basis for governance particularly in the African environment.[147] They argue that there are undoubtedly situations in which HHGE uses that fall under the categories of 'non-therapeutic' or 'enhancement'—according to some broader meanings of those terms—would be deemed acceptable by the

[142] S Hendriks and others, 'Reasons for Being in Favour of or against Genome Modification: A Survey of the Dutch General Public' (2018) 3 *Human Reproduction Open* 1, 6.
[143] ibid 7.
[144] Donrich Thaldar, Bonginkosi Shozi and Tamanda Agatha Kamwendo, 'Culture and Context: Why the Global Discourse on Heritable Genome Editing Should Be Broadened from the South African Perspective' (2021) 4 *BioLawJournal –Rivista di BioDiritto* 414.
[145] See https://knoema.com/atlas/Netherlands/Incidence-of-tuberculosis, accessed 12 December 2022.
[146] Thaldar, Shozi and Kamwendo op cit note 144 at 414.
[147] Thaldar et al op cit note 130 at 15.

public. This implies that decision-making by policymakers should be on a case-by-case, context-specific analysis and not where they lie in the therapy-enhancement binary.[148]

Therefore, the South African study results discussed in this chapter reveal that participants are generally receptive to the use of HHGE for immunity against the epidemics South Africa is challenged with. Therefore, there is need to ensure that the use of HHGE is not so overly regulated as to stifle enjoyment of these scientific discoveries. It was also uncontested during the deliberations that the government should devote resources to advancing HHGE research and ensuring equal access to HHGE healthcare services.[149] Scientific endeavour should be for the greater good and thus genetic technologies should be considered as part of a package of solutions for global challenges such as epidemics.

VI. CONCLUSION

This chapter familiarised the reader with the origins of the right of science and its direct implications on other rights, notably, the right of access to healthcare.[150] While the right of access to healthcare is becoming the focal point for human rights bodies and in academic circles regarding TB treatment, very few have explored the application of the right to science in enhancing TB treatment research.[151] For a disease like TB, which is mostly characterised by drug resistance, fulfilling the right of access healthcare requires the government to invest in scientific research. Since the right to benefit from scientific progress is not expressly provided for in our Constitution, I suggest how the right to culture/ cultural relations may be interpreted to give effect to the right to benefit from scientific progress. Based on the DPE study results, it also becomes clear that the general public is not outrightly rejecting the use of HHGE, provided some safety concerns are addressed. Most importantly, it has been discussed in this chapter that modifying the human genome to prevent children from contracting infectious disease such TB may or may not be regarded as genetic enhancement, depending on context and the severity of the disease in that particular nation. Therefore, it is crucial that any proposed global governance strategy on heritable genome editing be sufficiently comprehensive to account for these differences.

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[148] ibid.
[149] ibid 16–17.
[150] Yvonne Donders, 'The Right to Enjoy the Benefits of Scientific Progress: In Search of State Obligations in Relation to Health' (2011) 14(4) *Medicine, Health Care and Philosophy* 371.
[151] Mike Frick, Ian Henry & Erica Lessem, 'Falling Short of the Rights to Health and Scientific Progress: Inadequate TB Drug Research and Access' (2016) *Health and Human Rights Journal* 1.

CHAPTER 3

SHOULD WE BE CAUTIOUS IN PROMOTING THE RIGHT TO HUMAN GENOME EDITING FOR TREATING TB?

'An ounce of prevention is worth a pound of cure'– **Benjamin Franklin**

I. INTRODUCTORY REMARKS

As much as human genome editing promises immeasurable health benefits to society, it also poses the risk of harm to both the current and future generations. In permitting human genome editing, particularly germline editing, the irreversibility of such a decision becomes a significant aspect to act responsibly towards the current and future generations. The ability of humans to alter the human genome using gene-editing technology raises significant issues associated with among others the precautionary principle. Accordingly, this chapter provides reasonable explanations of the precautionary principle and, to defend the precautionary principle against some common criticisms, proposes guidelines on how the precautionary principle ought to be applied in the context of human genome editing so as not to unnecessarily stifle its clinical translation.

II. THE PRECAUTIONARY PRINCIPLE

The precautionary principle is a risk management tool used by policy makers in protecting health and the environment to ensure that people bear responsibility for potential damage to health by acting before there is strong proof of harm to avoid or reduce such threats to health.[1] The precautionary principle has a long history in public health and medicine. The principle provides that if an action or policy has a suspected risk of causing severe harm to the public domain, the action should not be taken in the absence of scientific near-certainty about its

[1] Fourth Ministerial Conference on Environment and Health Working paper: Dealing with uncertainty – how can the precautionary principle help protect the future of our children? (2004), available at http://www.tekno.dk/wp-content/uploads/2019/01/p04_boernene_og_miljoet-Dealing_with_uncertainty-WHO_april_2004.pdf, accessed 10 May 2019.

safety. The Rio Declaration on Environment and Development of 1992[2] defines the precautionary principle as:

> 'Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation'[3]

As precaution has moved into legal and political contexts, it has taken on slightly different meanings, each emphasising a particular aspect. The precautionary principle works along a continuum from relatively weak formulations that protect the status quo to very strong formulations.[4] Sceptics claim that there is no single principle but droves of differing versions, hence its popularity is derived from its vagueness. Stone argues that the precautionary principle fails to bind anyone to anything, and it does not resolve any of the deep dilemmas with which policymakers are faced.[5] Freestone in Stephen Gardiner observed cogently that while there is rapid adoption of the precautionary principle, no one is quite sure about what it really means, or how it is to be implemented.[6] Bodansky further argues that the precautionary principle is too blunt an instrument to be a regulatory standard. He argues that the principle does not stipulate what threshold of risk should warrant its application and how much caution should be taken.[7] Morodi questions whether the vagueness of the precautionary principle should result in its abandonment. He negates this by pointing out that the lack of precision in the definition is not unique to the precautionary principle but also holds in regard to several other decision rules.[8]

In 2000, the European Commission[9] released a communication on the precautionary principle,[10] attempting to give guidelines on its use and application. It aimed to prevent the

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[2] Rio Declaration on Environment and Development, available at http://www.unep.org/Documents/Default.asp?DocumentID=78&ArticleID=1163, accessed 30 September 2019.

[3] Fourth Ministerial Conference on Environment and Health Working paper: Dealing with uncertainty – how can the precautionary principle help protect the future of our children? (2004), available at http://www.tekno.dk/wp-content/uploads/2019/01/p04_boernene_og_miljoet-Dealing_with_uncertainty-WHO_april_2004.pdf, accessed 10 May 2019.

[4] Andrew Jordan & Timothy O'Riordan, 'The Precautionary Principle: A Legal and Policy History', *The precautionary principle: protecting public health, the environment and the future of our children* (WHO 2004) 37.

[5] C Stone, 'Is There a Precautionary Principle?' (2001) 7 *Environmental Law Reporter* 108.

[6] Stephen M Gardiner, 'A Core Precautionary Principle' (2006) 16(1) *Journal of Political Philosophy* 30.

[7] D Bodansky, 'Scientific Uncertainty and the Precautionary Principle' (1991) 33 *Environment* 43–45.

[8] Thabiso John Morodi, 'The Precautionary Principle and Public Environmental Decision-Making in South Africa: An Ethical Appraisal' (PhD, Stellenbosch University 2016) 53.

[9] This is an executive branch of the European Union tasked with proposing legislation and implementing decisions of Parliament. See https://europa.eu/european-union/about-eu/institutions-bodies/european-commission_en, accessed 30 September 2019.

[10] Communication from the Commission on the precautionary principle, available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A52000DC0001, accessed 30 September 2019.

arbitrary use of the precautionary principle since it is usually invoked without waiting until all the necessary scientific knowledge is available. Under the communication, the precautionary principle applies when 'scientific information is insufficient, inconclusive or uncertain or where there are indications that the possible effects…may be potentially dangerous and inconsistent with the chosen level of protection.'[11] Van de Belt argues that the European approach is flawed in that it does not state how scientific risk assessment and applying risk management principles should be applied in the absence of certain scientific data.[12] Secondly, there is no threshold on what should amount to a triggering action, such that even the slightest indication that a particular activity might possibly produce some harm to human health may suffice in invoking the principle.[13] Charles Weiss agrees, stating that the precautionary principle has allowed a wide range of risk acceptance or aversions due to its failure to specify the standard of proof to be applied to scientific evidence.[14] He describes the principle as an effective tool for blocking projects by failing to address the fact that most decisions involve a choice among alternatives, all of which involve benefits, costs, and risks and no alternative is risk-free.[15]

However, the US Supreme Court held in the *Benzene* case[16] held that OSHA cannot regulate on the basis of mere conjecture about uncertain risks and that the agency must demonstrate 'significant risk' before regulating.[17] The US approach, therefore, dictates that if no risks about a product have been demonstrated then it should be permitted. This is contrary to the European approach which handles risk not only as actual damage but also the possibility thereof. The US risk assessment is based on sound science, while the EC emphasises that all appropriate scientific data, including inadequate and incomplete data, be considered.

Conversely, in his article on the US-EU dispute and the precautionary principle,[18] Henk van den Belt introduces the strong version of the precautionary principle known as the zero-risk or catastrophe principle, which invokes the precautionary principle at the mere prospect of potentially harmful effects of a new technology. He argues that opponents of gene editing of

[11] E Fischer, 'Precaution, Precaution Everywhere: Developing a Common Understanding of the Precautionary Principle in the EC' [2002] Maastriht Journal of European and Comparative Law 7–28.
[12] Henk van den Belt, 'Biotechnology, the US-EU Dispute and the Precautionary Principle' 191 <https://edepot.wur.nl/137331> accessed 25 May 2021.
[13] ibid.
[14] Charles Weiss, 'Scientific Uncertainty and Science-Based Precaution' (2003) 3(2) *International Environmental Agreements: Politics, Law & Economic* 138.
[15] ibid.
[16] *Industrial Union Department v American Petroleum Institute*.
[17] JB Wiener & MD Rogers, 'Comparing Precaution in the United States and Europe' (2002) 5(4) *Journal of Risk Research* 317–349.
[18] van den Belt op cit note 12 at 192–193.

crops are more likely to use this version as zero-risk can never be achieved. Thus, a coherent implementation of this version of the precautionary principle would ultimately suppress all innovation by shifting the burden to biotech businesses, placing them completely at the mercy of regulatory bodies asking for ever-increasing safety assurances.[19] The catastrophe version of the precautionary principle neglects the costs of not continuing with the research despite the risks of doing it. The precautionary principle in this instance would shift from being an instrument for risk management to a political one.

Regardless of the specific application of CRISPR-CasX one might envisage, significant issues about possible risks to human health are likely to occur because the consequences of germline gene editing remain uncertain.[20] Gene editing is arguably a dual-use technology. It has the possibility of making highly targeted changes to genomes bringing about great health benefits, but at the same time the uncertainty about possible harm that may result from large-scale gene editing or from misuse of the technology raises great concerns. While a widespread precautionary approach to human genome editing regulation is justified, the precautionary approach must be interpreted to prevent a disproportionate focus on potential damage rather than potential advantages.

Risk analysis has often been used to make decisions by relying on scientific knowledge's certainty and objectivity. Wickson argues that with the precautionary principle, a new approach to decision-making that acknowledges and handles the full range of types of incertitude is adopted.[21] In a precautionary appraisal of medical risks, it is the norm that it is more desirable to prevent false negatives in risk assessments than false positive ones. That is; in assessing the relationship between harm and a particular activity, there is a preference in discovering a relationship that does not exist (false positive) than not to discover one that is fact there (false negative).[22] This is justified because the objective of a medical risk assessment is not to provide veracious medical facts but to safeguard patients against medical risks. Hence, the consequences of falsely believing that human genome editing is dangerous are seldom

[19] ibid 194.
[20] A Nordberg, T Minssen and SH Holm, 'Cutting Edges and Weaving Threads in the Gene Editing Evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns' [2018] *Journal of Law and the Biosciences* 48.
[21] F Wickson, 'Australia's Environmental Regulation of Genetically Modified Organisms: Risk and Uncertainty, Science and Precaution' 2005 *Griffith Journal of the Environment*.
[22] M Peterson, 'Should the Precautionary Principle Guide Our Actions or Our Beliefs' (2007) 33 *Journal of Medical Ethics* 7.

catastrophic whereas the consequences of falsely believing human genome editing to be safe when it is not might be catastrophic.[23]

Authors like Savulescu have also attempted to apply several versions of the precautionary principle to germline gene editing. They suggest the sufficientarian precautionary principle (SPP), which dictates that interested parties should take precautions against threats to achieving or maintaining a sufficient level of well-being.[24] In this view, human genome editing might be worth undertaking only when the level of wellbeing without intervention is low. This is problematic because it automatically eliminates germline gene editing for eugenic purposes. Even if it is so reserved for therapeutic purposes, gene editing always carries some risk of harm, the question then becomes what medical conditions will be considered as benign to affect an individual's level of well-being to have human genome editing worth trying.

It has also been argued that in circumstances of poorly understood risks such as those of gene editing, the Rawlsian core precautionary principle' (RCPP) is the appropriate principle to apply.[25] This version of the precautionary principle, as defined by Gardiner, is designed to address precisely those contexts in which we cannot attribute probabilities to the potential results of our actions either because we do not know what threats are posed by the activity or we lack an adequate basis from which to estimate the likelihood that the particular threats will eventuate. However, Koplin et al rightly point out that the RCPP can provide guidance only in scenarios where the probabilities of harm or benefit are highly uncertain. Therefore, this version may only apply to germline gene editing while the risks remain uncertain and unquantified. This version will become extraneous as more scientific data is made available pointing to the risks and benefits of germline gene editing.[26]

[23] ibid 7–9.
[24] JJ Koplin, C Gyngell and J Savulescu, 'Germline Gene Editing and the Precautionary Principle' [2019] *Bioethics* 8–9.
[25] ibid 7.
[26] ibid 8.

a) Core elements of the precautionary principle

The emergence of gene-editing technology has brought about the possibility of novel and efficient TB therapies. However, establishing and communicating the safety of human genome editing has caused controversy as most countries continue to show hesitancy to this novel technology. Precaution, or the idea of acting in precautiously beforehand to avoid something harmful from occurring is a common and reasonable approach as expressed in old folk wisdom — 'Better be safe than sorry'.[27] The precautionary principle entails that action ought to be taken to avoid or minimise unpredictable harms to people that may be brought about by a new technology like human genome editing. The precautionary principle has no universally accepted definition, however, a standard formulation is 'when an activity raises threats of harm to human health …, precautionary measures should be taken even if some cause and effects relationships are not fully established scientifically.'[28]

Principle 15 of the Rio Declaration on Environment and Development of 1992[29] has also defined the precautionary principle as:

> 'Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.'[30]

At an abstract level, the precautionary principle can be said to be a risk management tool that may assist in making healthcare decisions regarding human genome editing as the science is relatively new to medicine and there is a deficiency in scientific data from which to assess the risk of significant side effects that may manifest years after its initial clinical application. However, the precautionary principle has been subject to various academic risk and policy debates for being vague and incoherent. That is, the existing definitions of the precautionary

[27] Malintorn Puntuyakorn, 'A Comparative Study of the Precautionary Principle in Food Safety Laws and Regulations in the United States of America and the European Union' (2019) 9 *Thammasat Business Law Journal* 312.

[28] Marko Ahteensuu, 'Defending the Precautionary Principle Against Three Criticisms' (2007) 11(61/56) *Trames* 366.

[29] Rio Declaration on Environment and Development, available at *http://www.unep.org/Documents/Default.asp?DocumentID=78&ArticleID=1163*, accessed 30 September 2019

[30] 'Fourth Ministerial Conference on Environment and Health Working Paper: Dealing with Uncertainty – How Can the Precautionary Principle Help Protect the Future of Our Children?' <http://www.tekno.dk/wp-content/uploads/2019/01/p04_boernene_og_miljoet-Dealing_with_uncertainty-WHO_april_2004.pdf> accessed 17 May 2021.

principle do not specify the particular circumstances that must be met before it can be used, nor the type of preventative measures that must be taken.[31]

Fisher suggests that there are 'countless different legal and policy definitions … and endless examples of where it has been explicitly put into operation.'[32] This then raises the question of whether we should make use of such an ambiguous principle in guiding our societal actions. As will be illustrated, there are different versions of the precautionary principle with varying degrees of conservatism.[33] Put differently, the different formulations of the precautionary principle — ranging from weak to strong versions — speak to the level of protection that is to be implemented.

The weak versions of the precautionary principle are the least restrictive in that they allow for precautionary measures in the face of uncertainty but without necessarily imposing the need to implement them. For example, a weak version of the precautionary principle formulated in a *Lancet* editorial was cited by Douglas as follows:

> 'We must act on facts, and on the most accurate interpretation of them, using the best scientific information. That does not mean that we must sit back until we have 100% evidence about everything. Where the state of the health of the people is at stake, the risks can be so high and the costs of corrective action so great, that prevention is better than cure. We must analyse the possible benefits and costs of action and inaction. Where there are significant risks of damage to the public health, *we should be prepared to take action* to diminish those risks, even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it.'[34]

I highlight the use of the word 'should' as opposed to 'must' in the above formulation. In ordinary grammatical meaning, the word 'should' expresses advisability whereas the use of the word 'must' expresses an unavoidable obligation. Consequently, the use of the word 'should' in the formulation cited above, recommends relevant stakeholders to take precautionary measures even when the scientific knowledge is not conclusive but does necessarily compel them to take such measures. Accordingly, under the weak formulations, the necessity to justify

[31] van den Belt op cit note 12 at 191.
[32] E Fisher, 'Precaution, Precaution Everywhere: Developing a "Common Understanding" of the Precautionary Principle in the EC' (2002) 9(7) *Maastriht Journal of European and Comparative Law* 13.
[33] J Hughes, 'How Not to Criticize the Precautionary Principle' (2006) 31(5) *Journal of Medicine and Philosophy* 449.
[34] Douglas L Weed, 'Precaution, Prevention, and Public Health Ethics' (2010) 29(3) *Journal of Medicine and Philosophy* 316.

taking action (taking precautionary measures) generally falls on those advocating for precautionary action.

The strong variants of the precautionary principle, on the other hand, differ from the weak variants in that they reverse the burden of evidence.[35] This necessitates that before permission is given, persons proposing an activity must demonstrate that the technology is sufficiently safe. In the case of human genome editing, the strong version of the precautionary principle necessitates that the party who intends to engage in human genome editing must prove that it is harmless. An example of a strong formulation of the precautionary principle can be found in the Earth Charter of 2000 which stipulates that

> 'When knowledge is limited apply a precautionary approach … Place the burden of proof on those who argue that a proposed activity will not cause significant harm, and make the responsible parties liable for environmental harm'[36]

The precautionary approach adopted in the Earth Charter seems to be the most commonly adopted, which is why is it often argued that the precautionary principle stifles innovation. That is, in the absence of evidence proving the contrary, the precautionary principle acts as a constraint to innovation or development. Accordingly, in the absence of scientific evidence proving the safety of human genome editing, the precautionary principle can halt its clinical translation until proven otherwise. Similarly, the WHO Background Paper Governance on Human Genome Editing states that 'the precautionary principle should be respected, ensuring that substantial consensus of the scientific community on the safety of new technological applications be the premise for any further consideration.'[37] This entails that in the absence of substantial consensus, the precautionary principle may totally prohibit germline editing. However, in arguing that the precautionary principle is excessively conservative and thus stifles innovation, such criticism must be directed to a specific formulation of the precautionary principle — the strong versions — as this argument may not be extended to the weaker formulations.[38]

Accordingly, while the weaker versions of the precautionary principle enable the government to regulate risks in the face of scientific uncertainty, the stronger versions of the

[35] Morodi op cit note 8 at 1.
[36] ibid 2.
[37] Emmanuelle Tuerlings, 'WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing' 28 <https://www.who.int/ethics/topics/human-genome-editing/WHO-Commissioned-Governance-1-paper-March-19.pdf> accessed 13 May 2021.
[38] Hughes op cit note 33 at 449.

precautionary principle dictate that adopting precautionary measures should be a default reaction to threats of harm in the face of scientific uncertainty. Morodi also suggests that 'the strong version of the precautionary principle represents an affirmative call to action, while the weak version … represents something like a 'ceasefire' while negotiations are continuing.'[39] In its weakest form, the precautionary principle would stand for giving human genome editing a green light in the face of uncertainty, whereas the stronger versions of the precautionary principle would give it a red light. Furthermore, in some instances other forms of the precautionary principle would typically fall midway — moderate versions — by inviting an amber light — 'proceeding with caution'.[40] For instance:

> 'The participants … will continue to apply the precautionary principle, that is to take action to avoid potentially damaging impacts of substances that are persistent, toxic, and liable to bioaccumulate even where there is no scientific evidence to prove a causal link between emissions and effects.'[41]

However, the existing numerous formulations and definitions of the precautionary principle all present similar challenges: Is it ever possible to have complete scientific certainty in the case of emerging health technologies? Is there a minimum level of scientific certainty that must be achieved before proceeding with human genome editing? As a starting point, it should be noted that while there are official formulations of the precautionary principle such as the formulation by the Rio Declaration on Environment and Development, attempts to define and outline the ambit of this principle have mostly been undertaken in scholarly literature.[42]

Based on the Rio Declaration formulation of the precautionary principle cited earlier, precautionary measures should be taken even if the causal relationship between the activity and risks has not been fully established. On that account, if the primary purpose of the precautionary principle is to avert risk, how then do we improve on preventing future harm caused by human genome editing for instance if we do not really understand the causal link? Is this then not a misapplication of the precautionary principle itself? More so, there is no set minimum threshold of what the 'triggering action' should satisfy before the precautionary principle is invoked.

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[39] Morodi op cit note 8 at 2.
[40] Verna Jans, Wybo Dondorp & Sebastiaan Mastenbroek, 'Between Innovation and Precaution: How Did Offspring Safety Considerations Play a Role in Strategies of Introducing New Reproductive Techniques?' (2020) *Human Reproduction Open* 5.
[41] The Third International Conference on the Protection of the North Sea, Ministerial Declaration, 1990. See Deborah C Peterson, 'Precaution: Principles and Practice in Australian Environmental and Natural Resource Management' 8 <https://www.pc.gov.au/research/supporting/precaution/precaution.pdf> accessed 10 June 2021.
[42] Ahteensuu op cit note 28 at 369.

This entails that even the smallest indication that human genome editing might cause harm to human health is sufficient to invoke the precautionary principle.

The most important question is whether the precautionary principle should be abandoned because of its ambiguity. Perhaps not. According to Jordan and O'Riordan, the vagueness of the principle itself may in fact be a precondition to its functionality. They suggest that 'paradoxically, we conclude that the application of precaution will remain politically potent so long as it continues to be tantalisingly ill-defined and imperfectly translatable into codes of conduct …'[43] In their opinion, it is only through constant debate and critique of the precautionary principle that we may be able to formulate a workable version of the precautionary principle. Furthermore, Sandin et al argue that the lack of coherence in formulating the precautionary principle is in fact not unique and applies to many other principles as well. As a result, an identical argument should be presented to the other principles as well.[44]

Still, one would wonder whether it would not be ideal to place a 'moratorium' on the principle itself until we formulate a workable version as argued by Jordan and O'Riordan. As per Ronald Dworkin's definition of legal principle,

> 'a principle … states a reason that argues in one direction, but does not necessitate a particular decision …There may be other principles or policies arguing in the other direction … All that is meant, when we say that a particular principle is a principle of our law, is that the principle is one which office also must consider, if it is relevant, as a consideration inclining in one direction or another.'[45]

Stemming from this description, Dworkin illustrates that principles do not have to be formulated concretely. In fact, the ambiguity of the precautionary principles leaves room for discretion. What is important is the precautionary principle's core idea that it would be too late to wait for scientific certainty before responding to possible negative consequences of a new technology. Therefore, to argue that the precautionary principle should be abandoned on the basis of its ambiguity is a futile exercise as it necessitates one to demonstrate why the

[43] A Jordan & T O'Riordan, 'The Precautionary Principle in Contemporary Environmental Policy and Politics', *In Protecting public health and the environment: implementing the precautionary principle* (Island Press 1999) 18.
[44] P Sandin and others, 'Five Charges against the Precautionary Principle' (2002) 5 *Journal of Risk Research* 289.
[45] R Dworkin, *Taking Rights Seriously* (Harvard University Press 1978) 26.

precautionary principle's case is different and more problematic as compared to other principles.

b) When should the precautionary principle be applied?

The question is whether to act given the current TB epidemic. More precisely, this question begs selecting between a number of alternative actions, one of which is not to act. The other alternatives would be to give human genome editing the green light but to apply varying degrees of restriction. This entails analysing the consequences of each alternative action, including inaction.[46]

In deciding whether to act, the question should not be understood as not whether to restrict or ban human genome editing, but rather whether to apply the precautionary principle. Understanding how and why the precautionary principle should be applied necessitates a thorough understanding of scientific uncertainty.[47] It is often argued that the definition of the word 'uncertainty' is even more complicated than it seems. As rightly pointed out by the European Commission, uncertainty can stem from a number of factors, among others;

> '… from more than a simple lack of data or inadequate models of risk assessment. Uncertainty might also exist in the form of indeterminacy (where we don't know all the factors influencing the causal chains), ambiguity (where there are contradictory certainties), and ignorance (where we don't know what we don't know).'[48]

The primary objective of public health and precaution is to prevent diseases, threats to human health, as well as to restore healthy conditions. However, there is no standard procedure or set of guidelines for determining when and how to apply the precautionary principle in specific situations. Balancing is therefore required in determining what degree of protection is appropriate while at the same time not interfering excessively with a person's rights and liberties.[49] If a government wishes to limit or restrict the use of CRISPR for human genome editing because of its potentially harmful consequences or uncertainty, democratic society's commitment to the value of freedom demands that the reason must be sufficiently compelling to justify the limitation or restriction. As a consequence, the reason for limiting or restricting

[46] Karsten Klint Jensen, 'The Moral Foundation of the Precautionary Principle' (2002) 15 *Journal of Agricultural and Environmental Ethics* 48.
[47] European Commission, 'The Precautionary Principle: Decision-Making under Uncertainty' 5 <https://ec.europa.eu/environment/integration/research/newsalert/pdf/precautionary_principle_decision_making_under_uncertainty_FB18_en.pdf> accessed 13 May 2021.
[48] ibid.
[49] Jensen op cit note 46 at 41.

the use of CRISPR must be based on sufficient scientific evidence as well as the severity and frequency of the harm in question.[50]

Over and above that, one of the common criticisms against the stronger versions of the precautionary principle is that they stifle innovation. This criticism is based on the premise that it is impossible to completely eliminate risk — there is no such thing as a zero-risk activity. In the case of germline editing, the risks involved would befall those who undergo germline intervention and their progenies. However, there is no such thing as a risk-free medical intervention, and adverse reactions will inevitably occur in some cases, even when all reasonable precautions are taken. Yet, the reassurance that the chance of serious side-effects is extremely slim remains unfathomable abstract to certain parents and the society at large. The most asked question would be: What if it turns out that my child is the one that experiences the extremely rare but severe side effects?

Although Persson argues that exercising 'extra precaution' may be justified when dealing with health issues,[51] I posit that the belief that human genome editing should only be permitted if it results in perfectly modified offspring clearly sets the bar too high. Not only do all medical interventions come with risks, but a careful analysis should also be made to ascertain if the risks involved greatly outweigh the benefits. However, it is also important to highlight that depending on one's experiences with TB, some parents would be willing to accept even high risks for their progenies as opposed to exposing them to the risk of contracting TB should it be left to the individual parents to decide on what degree of risk of harm should be acceptable.

Although widely adopted as a risk management tool, one may argue that the different formulations of precautionary principle generally lack an accepted array of guidelines to guide its implementation. Because of the arbitrary manner in which the precautionary principle is applied, the precautionary principle itself must be approached with 'precaution'. The use of the precautionary principles irrespective of the formulation may give rise to a number of negative consequences. First, the precautionary measures adopted may give rise to new health concerns. Gregory Conco argues that 'if the precautionary principle had been applied decades ago to innovations like polio vaccines, and antibiotics, regulators might have prevented occasionally serious, and sometimes fatal, side effects by delaying or denying approval of those products, but that precaution would have come at the expense of millions of lives lost to infectious

[50] ibid 43.
[51] E Persson, 'What Are the Core Ideas behind the Precautionary Principle?' (2016) 557– 558 *Science of the Total Environment* 131–133.

diseases'[52] While the precautionary principle directs us to avoid or prolong the introduction of potentially harmful new activities to avoid harm to humans, the postponement itself may create harm in its own right. Authors such as Hughes have even argued that the precautionary principle should actually caution us from adopting it – at least its strong version – to avoid this harm.[53] I do not agree with this argument and would suggest that society should abstain from the very strong formulations of the precautionary principle to avoid creating the harm aforementioned.

Society ought to be careful in that a misapplication of the precautionary principle that could jeopardise one of the most fundamental liberties guaranteed by the South African Bill of Rights — the right of access to healthcare services. That is, the precautionary principle should be applied cautiously not to give an absolute ban to human genome editing. More so, in the context of South Africa, the question is how to apply the precautionary principle to public health matters such as these.

The Preamble of the National Health Act states that

> 'RECOGNISING- … the need to heal the divisions of the past and to establish a society based on … the need to improve the quality of life of all citizens and to free the potential the past; democratic values, social justice and fundamental human rights; … BEARING IN MIND THAT- … in terms of section 24(a) of the Constitution everyone has the right to an *environment* that is not harmful to their health or well-being' [my emphasis]

Furthermore, section 2(c)*(ii)* of the Act provides that one of the objects of the Act is to 'regulate national health … by protecting, respecting, promoting and fulfilling the rights of the people of South Africa to an *environment* that is not harmful to their health or well-being ….' [My emphasis] Thus, if a health officer has sufficient grounds to believe that a person is in violation of section 24(a) of the Constitution, such person may be ordered to take necessary corrective action in to minimise, remove or rectify such threats.[54]

To unravel the legislator's intentions and shed light on the applicability of the precautionary principle under the National Health Act, it is useful to go back to the position of the precautionary principle in environmental matters in South Africa. The Constitutional Court in an environmental-related case of *Fuel Retailers Association v Director-General:*

[52] Gregory Conco, 'Safety, Risk and the Precautionary Principle: Rethinking Precautionary Approaches to the Regulation of Transgenic Plants' (2003) 12 *Transgenic Research* 100.
[53] Hughes op cit note 33 at 448–449.
[54] National Health Act s 83(1)(a).

Environmental Management drew attention to the role of environmental authorities in averting threats of contamination to underground water supply caused by the proposed construction of a filling station. The court in concluding its judgment stated that 'the precautionary principle [my emphasis] … is applicable where, due to unavailable scientific knowledge, there is uncertainty as to the future impact of the proposed development. Water is a precious commodity; it is a natural resource that must be protected for the benefit of present and future generations.'[55] Thereby, this indicates that in environmental matters, the precautionary principle is recognised as a vital constituent in the decision-making process of all proposed innovations tainted with scientific uncertainty regarding risk to the environment. A closer look into South African environmental legislation also reveals that most environmental legislations have the hallmarks of a precautionary approach to risk.[56] As a result, the precautionary principle provides an essential policy basis for anticipating, avoiding, and mitigating environmental problems in South Africa.

Can it be concluded, then, that the legislator's inclusion of environmental issues as determinants of overall health and well-being of the people, also aimed to embrace the precautionary principle in health law? Perhaps not. In my view, the precautionary principle will only apply to the extent that health law relates to some aspect of the environment as was the case in the *Fuel Retailers Association* case. Access to safe water has a direct bearing on health and hence the contaminated water could have jeopardised both the physical and social health of the people.

However, it is worth noting that risk assessment is most effective when scientific data is nearly complete — minimal uncertainty.[57] Whereas, the precautionary principle should be understood to be based on the necessity to take precautionary measures due to scientific uncertainty, and not in spite of scientific uncertainty.[58] Therefore, since risk assessment will most likely fail to adequately address uncertainty and provide direction in complex medical innovations such as human genome editing, it may be inferred that the precautionary principle would be applicable in this instance. As discussed earlier, harm to human health may occur

[55] *Fuel Retailers Association of Southern Africa v Director-General: Environmental Management* (2007 6 SA 4 (CC)) [98].
[56] Such as the National Water Act, Act No 36 of 1998, the new National Environment Management: Air Quality Act, Act No 39 of 2004, and the Occupational Health and Safety Act, Act No 85 of 1993. See Morodi op cit note 8 at 10.
[57] Philippe Grandjean, 'Implications of the Precautionary Principle for Primary Prevention and Research' (2004) 25 *Annual Review of Public Health* 203.
[58] Jason Maclean, 'Principle 5 - Precautionary Principle', *Corporate Social Responsibility: A Legal Analysis* (LexisNexis 2009) 370.

from intervening, as well as from not acting. The aim is therefore to evaluate public health interventions with the aid of the precautionary principle to make decisions in favour of interventions that improve population health.

Arguably, adopting the weaker versions of the precautionary principle by South Africa would pave a way for a more workable solution than adopting the stronger version in addressing South Africa's TB epidemic as the onus would then be placed on those who seek to limit the clinical translation of gene-editing technology to provide substantive evidence of the threats of harm that gene editing presents to human health. With the weak formulations of the precautionary principle being highly pragmatic, relevant stakeholders have more leeway when it comes to deciding how various conflicting rights and interests should be weighted. This is because, as illustrated earlier in the chapter, the language in stronger versions is unmistakably stronger and may allude to more aggressive forms of action that ought to be taken[59] such as an outright ban until proponents of human genome editing demonstrate that gene-editing technology and its related procedures are (sufficiently) safe. Nevertheless, in deciding to apply the precautionary principle to public health, I suggest that it is important to develop a framework on how the precautionary principle should be applied. Accordingly, in the next section, I propose guidelines on the application of the precautionary principle to best serve South Africa's healthcare needs while at the same time minimising harm to its people.

c) Proposed guidelines on the application of the precautionary principle to human genome editing

Using the guidelines set out by the International Union for Conservation of Nature,[60] I propose eight guiding principles on how the precautionary principle should be applied with regards to human genome editing.

[59] Peterson op cit note 41 at 9.
[60] IUCN Council, 'Guidelines for Applying the Precautionary Principle to Biodiversity Conservation and Natural Resource Management' 5–11 <https://www.iucn.org/sites/dev/files/import/downloads/ln250507_ppguidelines.pdf>.

Guideline 1: Integration

This guideline calls for the international community not to assess the applicability of the precautionary principle to human genome editing in isolation. This necessitates the application of the precautionary principle with other relevant rights and principles. Put differently, in assessing whether to proceed with human genome editing, relevant stakeholders must consider other relevant rights and values such as the right of access to healthcare services, the right to human dignity, the principle of intra-generational justice and autonomy. In response, the precautionary principle should be applied on a case-by-case basis — the different applications of human genome editing. Consequently, these rights and principles, may in some cases, bolster the argument for taking precautionary measures. In other cases, the precautionary principle will have to be balanced against these other rights and values so as not to arbitrarily compromise the affected rights.

Guideline 2: Include stakeholders and right holders

In assessing the permissibility of human genome editing, particularly germline editing, all relevant stakeholders and right holders must be involved in the assessment, decision-making and implementation processes. As identified under Guideline 1, precautionary decision-making involves a balancing exercise with other rights and values. Therefore, not only must stakeholders and right holders be involved, the process of evaluation, decision-making, and execution must also be transparent. This will ensure that values, judgments and cultural perceptions of human genome editing are all taken into consideration. These relevant stakeholders also include those who bear the costs of the potential threat. As discussed earlier in the chapter, the risk is borne by those who undergo germline editing as well as their progenies.

This also entails including those who bear costs of precautionary action (a ban on germline editing for instance). Members of the local community should be given the opportunity and resources to voice their interests effectively, and this should not be precluded by technical, logistical, and language barriers. Fortunately, one of the guiding values and principles enshrined in the WHO Framework for Governance on Human Genome Editing is 'Inclusiveness, solidarity, and the common good'.[61] It calls for 'a commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different

[61] 'WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. Human Genome Editing: A Final Framework for Governance. 2021'.

social, cultural, and religious beliefs and moral values, skill sets'[62] to achieve a common good. Indeed, before a decision not to allow human genome editing for purposes of treating TB is made, it is only logical that the community most affected by the TB epidemic is involved in this decision-making process.

Guideline 3: Use the best available scientific data

Precautionary measures taken in light of human genome editing should be based on the best available scientific evidence. That is to say, when applying the precautionary principle, all available relevant information be taken into consideration, but the best available scientific information should be used. Efforts should be made to ensure the scientific data gathered is independent, unbiased, and collected transparently. This can be made easier by ensuring that information is collected by different agencies that are both autonomous and accountable to the public.

Guideline 4: Characterise the threats of harm

Characterise the risk(s) and assess the uncertainties surrounding human genome editing. The risks addressed should include not only risks directed to the current generation but also long-term risks, and the incremental impacts of human genome editing on subsequent generations. It is also important that attempts should be made to ascertain what is known and what is unknown concerning human genome editing as well as what knowledge can be improved and what cannot. This calls for appreciating areas of ignorance, uncertainty, information gaps, and the actual limitations of the methods used in detecting and assessing the risks and threats of harm.

Guideline 5: Assess all available options

Ascertain the available options for dealing with threats of harm posed by human genome editing, as well as the probable implications of each course of action or inaction. There should be a robust quest for precautionary measures and realistic solutions, as well as encouraging proactive steps to predict, avoid, and mitigate threats presented by human genome editing. Most importantly, it is necessary to weigh the advantages of delaying the clinical translation of human genome editing to gather scientific data to minimise uncertainty against the harm that such a delay can pose on other conflicting health interests.

[62] ibid.

Guideline 6: Proportionality

The precautionary measures adopted ought to be proportionate to the potential threats they seek to avert. The proportionality principle dictates that a reasonable balance must be struck between the stringency of the precautionary measures adopted and the seriousness and irreversibility of the potential risk of harm posed by human genome editing. According to the precautionary principle, precautionary measures should be initiated even in the absence of scientific data. It is based on an 'act-then-learn' strategy as opposed to the typical 'wait-and-see' strategy. Therefore, where precautionary measures are taken due to scientific uncertainty, the degree of uncertainty as proposed under Guideline 4 must also be considered in implementing the precautionary measures.

The study of cost-effectiveness or social-economic factors is another aspect of the proportionality principle. Measures based on the precautionary principle should be cost-effective, and countries should only follow the principle to the extent that they are capable of doing so. As a result, countries of varying economic and financial strengths are required to obey the precautionary principle in different ways.

Guideline 7: Be explicit

To avoid arbitrariness, — implementing measures that are not proportional to the risk being averted, — the uncertainty to which the precautionary measures are being adopted should be stated explicitly. This also calls for the need to be explicit about the exact precautionary measures adopted. This promotes accountability, as well as lays a solid foundation for monitoring and reviewing the measures implemented at a later time.

Guideline 8: Periodic review of measures implemented

Once the precautionary measures have been implemented, there must be a constant review of measures implemented in light of emerging scientific evidence. An adaptive approach that is aimed at promoting research to reduce key uncertainties through scientific discoveries is therefore encouraged. Interestingly, in the presidential conclusion to the European Council Meeting in Nice in December 2000, the following was stated:

> '...decisions taken in accordance with the precautionary principle should be reviewed in the light of developments in scientific knowledge. To that end the impact of such decisions should be monitored, and additional research conducted to reduce the level of uncertainty.'[63]

Accordingly, there needs to be a periodic evaluation of the initial measures implemented, the possible outcomes or drawing of lessons (if any), and the need to adjust accordingly. This is one of the most important guidelines as it ensures that even if disproportional precautionary measures may have been taken regarding the clinical application of human genome editing, regular periodic reviews afford relevant stakeholders an opportunity to revise their decisions in light of emerging scientific research on the threat or uncertainty being averted. Depending on the magnitude and content of new scientific evidence gathered, this may in some cases, lead to the precautionary measure no longer being needed thereby fostering a much quicker clinical translational pathway for human genome editing. Conversely, it may also lead to the conclusion that the risk presented by human genome editing is more severe than initially projected, necessitating more stringent precautionary measures to be adopted.

d) Can we or should we use gene-editing technology

i. The serious factor: Tuberculosis and gene editing

Although there are individuals who believe that any sort of genetic modification is immoral, this opinion is not generally held. Other bioethicists and scientists have accepted that germline editing might, in some circumstances, be ethically acceptable.[64] Perhaps the most important ethical issue about human genome editing is its potential clinical utility. Policy debates and legislative reforms around heritable human genome editing use the concept of a 'serious' disease as a key criterion for deciding which diseases should be targeted by gene editing technologies.[65] For instance, the National Academies/ Royal Society Report on Heritable Human Genome Editing suggests germline editing be limited to 'preventing a serious monogenic disease or condition' (Recommendation 4).[66] The report defines serious monogenic disease as 'one that causes severe morbidity or premature death.'[67] Panama and Finland also prohibit human germline editing (for reproduction) except where it is performed to treat,

[63] Nicolas Treich, 'What Is the Economic Meaning of the Precautionary Principle?' (2001) 26(3) *The Geneva Papers on Risk and Insurance* 336.
[64] Thaldar and others, 'Human Germline Editing: Legal-Ethical Guidelines for South Africa' (2020) 116 No 9/10 *South African Journal of Science* 3.
[65] Erika Kleiderman, Vardit Ravitsky & Bartha Maria Knoppers, 'The "Serious" Factor in Germline Modification' (2019) 45 *Journal of Medical Ethics* 508.
[66] National Academy of Science, National Academy of Medicine and The Royal Society.
[67] ibid.

prevent or eliminate serious hereditary illnesses.[68]Additionally, germline modifications for motives other than serious disease treatments is punishable by a two to six year prison sentence in Panama and Mexico.[69] Regardless the specific definition in the National Academies report, the concept of serious disease is very slippery and may delay the clinical translational pathway of human genome editing as its green light relies heavily on being able to distinguish a 'serious' disease.[70] However, due to the fluidity of the concept, it is argued that even endorsers of National Academies recommendation are unlikely to arrive at the same conclusion.[71]

Literature has demonstrated that there is extreme difficulty in drawing clear lines on what should be regarded as a serious disease.[72] Kleiderman et al explore the notion of 'serious' disease and aver that the definition of 'serious' should be broadened beyond a 'medical criterion' as suggested in the National Academies report by also accounting for changing social circumstances — societal impact and cost of disease treatment should also be taken into consideration.[73] It is argued that different societies will interpret the concept of serious disease in light of their unique historical, cultural, and social traits. This may be attributed to several factors, such as, the way certain diseases express differently in individuals as well as the individual and societal perceptions of the disease.[74] Despite the undefined nature of 'serious' rendering its application challenging and eventually arbitrary decision making, it is important to assess whether TB is so serious a disease that it warrants such a drastic step (human genome editing)? Such a question is complex and controversial.

South Africa has a staggering burden of TB infections and deaths. TB knows no race, age and social status. It is spread through the air when an infected person speaks, sings, or laughs, coughs, sneezes. Anyone can get TB! In 2019, an estimated 360,000 persons contracted TB and around 58 000 people died of TB in South Africa.[75] South Africa continues to carry the world's eighth highest burden of TB. Even more worrisome, the 2020 World TB Report also

[68] Françoise Baylis and others, 'Human Germline and Heritable Genome Editing: The Global Policy Landscape' (2020) 3(5) *The CRISPR Journal* 370.
[69] V Kalidasan & Theva Das Kumitaa, 'Is Malaysia Ready for Human Gene Editing: A Regulatory, Biosafety and Biosecurity Perspective' [2021] *Frontiers in Bioengineering and Biotechnology* 13.
[70] Kleiderman, Ravitsky & Knoppers op cit 65 at 508.
[71] National Academies of Sciences, *Human Genome Editing: Science, Ethics, and Governance* (National Academies Press 2017).
[72] ibid 7.
[73] Kleiderman, Ravitsky & Knoppers op cit note 65 at 509.
[74] National Academies of Sciences op cit note 71.
[75] Muhammad Osman and others, 'Health System Determinants of Tuberculosis Mortality in South Africa: A Causal Loop Model' (2021) 21 (388) *BMC Health Services Research* 2.

indicates that at least 20 per cent more people are falling ill with TB in South Africa.[76] South Africa is therefore coping with epidemics like TB on an unprecedented scale. Ultimately, the quality of life and consequently the dignity of South Africans are being undermined by the disease, which also disproportionately afflicts the poor, aggravating inequality.[77] The high TB mortality rates and the ineffective attempts to reduce South Africans' default on TB treatment (which frequently leads to multi-drug resistant TB) are morally compelling reasons for the state to give parents the chance to have children who will be resistant to TB.[78]

However, although TB affects people of all ages, in 2018, men aged ≥15 years had the largest burden, accounting for 57 percent of all TB related deaths.[79] In summary the table below illustrates an extremely high rate of mortality between 15 – 49-year-olds. While mortalities seem to be low in other age groups, it is clear that TB mortality is strongly age dependent thus the 15–49 age group might be an important target for germline intervention.

Table 1: Number and proportion of reported TB deaths by age group, 2010 – 2016[80]

	Age group (years), (n%)			
Year	**1-14**	**15-49**	**50-64**	**≥ 65**
2010	1 945 (3.1)	44 230 (70.5)	11 795 (18.8)	4 768 (7.6)
2011	1 402 (2.6)	36 719 (68.1)	10 999 (20.4)	4 799 (8.9)
2012	1 100 (2.5)	29 167 (66.3)	9 414 (21.4)	4 311 (9.8)
2013	767 (1.9)	21 640 (53.6)	13 444 (33.3)	4 522 (11.2)
2014	679 (1.8)	19 576 (51.9)	12 938 (34.3)	4 526 (12.0)
2015	494 (1.5)	16 329 (49.6)	11 753 (35.7)	4 346 (13.2)
2016	441 (1.5)	14 406 (49.0)	10 495 (35.7)	4 057 (13.8)

[76] Marcus Low, 'WHO Estimates 20% More TB Cases in SA than Previously Thought' *Spotlight* (14 October 2020) <https://www.spotlightnsp.co.za/2020/10/14/who-estimates-20-more-tb-cases-in-sa-than-previously-thought/> accessed 17 November 2021.
[77] Thaldar et al op cit note 64 at 3.
[78] Donrich Thaldar, Bonginkosi Shozi and Tamanda Agatha Kamwendo, 'Culture and Context: Why the Global Discourse on Heritable Genome Editing Should Be Broadened from the South African Perspective' (2021) 4 *BioLawJournal –Rivista di BioDiritto* 415.
[79] World Health Organization, 'WHO Global Tuberculosis Report 2019' <https://tbsouthafrica.org.za/resources/who-global-tuberculosis-report-2019> accessed 27 March 2021.
[80] M Loveday and others, 'Figures of the Dead: A Decade of Tuberculosis Mortality Registrations in South Africa' (2019) 109(10) *South African Medical Journal* 730.

ii. The collective good of herd immunity through germline editing

Although TB related deaths have reduced over the years, TB still endangers the lives of many people not only in South Africa, but around the world. The current TB strains will certainly not be the last and it is highly likely that there will be strains in the future, some which will be more contagious and deadly. How can we avoid epidemics in the future more efficiently and sustainably?

Herd immunity may be defined as 'a phenomenon where a fraction of resistant individuals in a population reduces the probability of transmission of a pathogen among the susceptible individuals.'[81] Put differently, when a disease such as TB spreads across a population, it comes across people that it is unable to infect and thus the TB epidemic is likely to come to an end if there are enough of these people.[82] At individual level, acquired immunity may be established through natural infection or through immunisation (vaccination).[83]

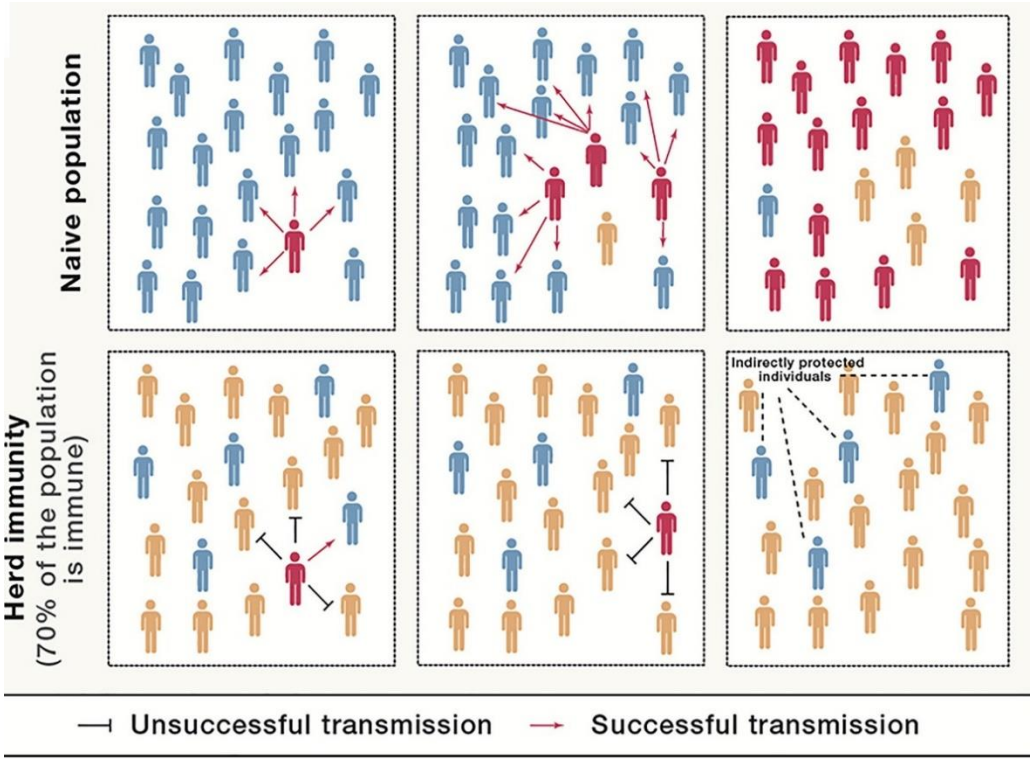

Figure 4: illustrating herd immunity[84]

[81] Pavel Payne and others, 'CRISPR-Based Herd Immunity Can Limit Phage Epidemics in Bacterial Populations' (2018) 7 *eLife* 1.
[82] ibid 2.
[83] Haley E Randolph & Luis B Barreiro, 'Herd Immunity: Understanding COVID-19' (2020) 52(5) *Immunity* 737.
[84] ibid 738.

The figure above illustrates the concept of herd immunity. Put it in the context of TB, when a TB infected person is introduced into a fully susceptible population (top panel), TB will spread rapidly. However, when an infected person is introduced into a population that has met the herd immunity threshold (bottom panel) through germline editing, the disease fails to spread.[85] Although there is an individual that is not resistant to TB, the population as a whole provides protection as there will be less high-risk people in the population, as a result, infection rates fall, and the disease eventually fades away.[86]

As a consequence, although there is some existing immunity to build on, the TB epidemic has already claimed so many lives in South Africa and we cannot simply wait for the greater population to acquire immunity through natural infection. How then do we reach the TB herd immunity threshold in the absence of an effective vaccine? I propose that the road to achieving herd immunity will take a hybrid approach. Germline editing is the only long-term solution for eradicating many highly contagious diseases such as TB from the list of health issues that future generations have to deal with. Human genome editing could provide a means of mitigating harms that have already set in motion for future generations.[87] The accelerated pace of achieving 'generational' herd immunity is what makes germline editing even more appealing and economically sustainable in the long-run. In a normal vaccine routine, each individual would need to be vaccinated including persons yet to be born. However, with germline editing, the current generation creates immunity even for generations yet to come.

Moreover, studies have shown that pregnant women are another group of people who are more likely to die from TB. Between 2014 and 2016, TB was responsible for 11% of maternal deaths in South Africa, and it is still one of the leading non-pregnancy-related infection that causes maternal death.[88] Hence, even though the priority for germline editing would logically be prioritised for those with the highest risk of mortality (15–49 age group), germline intervention on pregnant women may be another critical intervention, not only for their developing child's protection but to also support herd immunity.

As is argued above, germline gene editing could accelerate the pace at which we achieve herd immunity against TB. However, TB like many other diseases that germline gene editing

[85] ibid 737–738.
[86] Monica Neagu, 'The Bumpy Road to Achieve Herd Immunity in COVID-19' (2020) 41(6) *Journal of Immunoassay and Immunochemistry* 929.
[87] Christopher Gyngell, Hilary Bowman-Smart & Julian Savulescu, 'Moral Reasons to Edit the Human Genome: Picking up from the Nuffield Report' (2019) 45 *Journal of Medical Ethics* 4.
[88] Loveday op cit note 80 at 730.

could be appropriate for, can be remedied — at least to some extent through somatic editing (gene therapy).[89] This raises the question – is it not better to treat TB through somatic editing (gene therapy) and cause no harm to future generations? Is it worth manipulating genes of future generations?

The answer to this question is context-based and would largely depend on a case-by-case basis. By way of illustration, I shall use age as one of the deciding factors in determining the appropriate remedy. Given that very few people start families or even continue to have children in their 50s for instance, there is little reason to invest resources in editing the gametes of individuals in their 50s. As with all initiatives taken to emolliate TB, germline editing in this age group is only justifiable if the persons who undergoes such, continues to bear children thus creating 'generational herd immunity'. Thus, in weighing which of the two approaches to adopt, issues of efficacy become paramount. However, according to Table 1 above, persons within the 50–64 age group suffer the second highest TB fatalities and hence it would be justifiable to conduct gene therapy on these persons. The same applies to those over 65 years old.

Nonetheless, the answer would be different if the person for instance, is a 30-year-old female. Firstly, this female falls into the 15–49 age group which has the highest TB mortality as illustrated in Figure 3 therefore necessitating the need to undergo germline editing. Secondly, this female is still within the child-bearing age which also creates an additional potential to protect her offspring. Therefore, editing the eggs of woman (in vivo) who is of child-bearing age would assist in achieving the intended herd immunity thus making it a reasonable healthcare policy. All in all, human genome editing — germline or somatic — presents a trade-off in that the individual is protected, and society as a whole is safer.

In conclusion, there has been an oversight in acknowledging the extent to which the practical circumstances of the various nations, may justify a departure from what may be described as the mainstream global position on issues such as which applications of CRISPR ought to be allowed.[90] Accordingly, South Africa (and many other nations in a similar situation) would have a compelling reason to pursue heritable genome editing if it offers the promise of lessening the effects of this epidemic by giving parents the option to have children who are

[89] Bryan Cwik, 'Responsible Translational Pathways for Germline Gene Editing?' (2020) 6 *Current Stem Cell Reports* 129.
[90] Thaldar, Shozi and Kamwendo op cit note 78 at 413.

resistant to contracting TB.[91] However, the discussion in this chapter demonstrates that most researchers are against the use of the precautionary principle because it tends to tie their hands and thus stifles innovation and the use of beneficial technologies such as CRISPR. When in fact, the precautionary principle should serve as a risk management tool that creates a temporal space in which to consider the possibility of harm to humans. More so, there is a limit on how long the world should continue to explore the possibilities of harm posed by human genome editing. I suggest that there is need to take a leap forward at some stage through the clinical translation of human genome editing. Caution does not entail that genome editing should be prohibited, but rather proportional precautionary measures should be implemented. As such, the precautionary principle should be taken as 'looking both ways before proceeding through the yellow light' and hence we ought to heal whenever the opportunity arises. Invoking the precautionary principle should therefore be done on a case-by-case basis as has been demonstrated in the case of TB rather than as a general rule or regulation. It is also important to acknowledge that scientific advancement does not happen in a vacuum — it functions within a society. Therefore, relevant authorities must involve relevant stakeholders and right holders to promote exposure to different beliefs, doubts, rights and interests, and safety concerns within society.

[91] ibid 414.

CHAPTER 4

A RIGHT TO ACCESS TO HERITABLE HUMAN GENOME EDITING IN SOUTH AFRICA

*'You can't fight for your rights if you don't know what they are.' — **John Roberts***

I. INTRODUCTION

Access to healthcare remains an intractable challenge in the African region. One may reaffirm Meier's assertion that 'health is essential for human rights flourishing and the exercise of all other rights.'[1] To enforce or claim the right of access to healthcare services, it should be clearly defined. Accordingly, this chapter then conceptualises the right to heritable human genome editing in South Africa as falling within the ambit of the right of access to healthcare services. While access to gene editing technology is motivated by the Constitutional mandate under section 27, it must meet and pass Constitutional muster by meeting all tenets of the right of access to healthcare. Thus, principles such as social solidarity, effectiveness, equity, affordability, and efficiency are incorporated in discussing the right to heritable human genome editing.

In addressing this, this chapter is divided into four parts. Part II discusses the nature of the right to health in international instruments and its interpretation. Part III discusses the right of access to healthcare services as enshrined in our Constitution. Part IV crafts the right to human genome editing in South Africa as well as address the issue of limited CRISPR therapies and ultimately recommends rationing guidelines that will help ensure that the limited CRISPR resources reap the greatest good in society.

[1] Benjamin Mason Meier, 'The Highest Attainable Standard: Advancing a Collective Human Right to Public Health' (2005) 37 *Columbia Human Rights Law Review* 120.

II. THE NATURE OF THE RIGHT TO HEALTH

The right to health is comprehensive in that it covers all underlying determinations of health. Hence, the provision of healthcare is just one aspect of the right.[2] At the international level, the Universal Declaration of Human Rights (UDHR)[3] is the first international instrument to define what constitutes universal human rights. Although the Declaration is not a legally binding document, it still has significance as a turning point in the history of human rights and as the ethos that underpins human rights. The right to health is provided for in Article 25(1) of the Declaration which states:

> 'Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control.'[4]

It is significant to highlight that this formulation of the right to health places a strong emphasis on empowering individuals to achieve optimal health by having access to the necessary resources that will ensure a healthy life. This formulation of the right recognizes its reliance on social determinants of health in addition to healthcare. This also serves as a recognition of the interdependent nature of human rights. The right to health has also been included in several international instruments, such as the Convention on the Rights of the Child (CRC)[5] under Article 24, and Article 12 of the Convention on the Elimination of all Forms of Discrimination Against Women (CEDAW).[6]

While the UDHR is a declaration by participating State parties, the International Covenant on Economic, Social, and Cultural Rights (ICESCR) is the central instrument for the legal protection of socio-economic rights one of which is the right to health.[7] Article 12 provides that everyone has the right to the enjoyment of the highest attainable standard of physical and

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[2] J Bahar, 'The Justiciability and Enforcement of the Right to Health under the African Human Rights System' (2013) 2(1) *Haramaya Law Review* 29–45.

[3] The UN General Assembly, Universal Declaration of Human Rights, 10 December 1948, available at https://www.refworld.org/docid/3ae6b3712c.html (accessed October 31, 2022).'Article 25 The Universal Declaration of Human Rights'.

[4] Article 25

[5] UN General Assembly, *Convention on the Rights of the Child*, 20 November 1989, United Nations, Treaty Series, vol. 1577, p. 3, available at *https://www.refworld.org/docid/3ae6b38f0.html*, accessed 30 September 2019.

[6] UN General Assembly, *Convention on the Elimination of All Forms of Discrimination against Women*, 18 December 1979, A/RES/34/180, available at https://www refworld.org/docid/3b00f2244.html, accessed 30 September 2019.

[7] Ibid at Art 12.

mental health. Article 12 provides the most extensive provision on the right to health in international human rights law as it provides a broader extrapolation of the nature and content of the right to health by including steps to be taken by the States Parties to achieve the full realization of this right. Of relevance to this study is the obligation that State Parties take steps to ensure 'the prevention, treatment and control of epidemic, endemic, occupational and other diseases.'[8] The domain of the right to health shifts from the simple recognition of an individual's right to be healthy to one that requires States to not only respect and protect the right to health but also to take steps to realize it.

The right to health is a socio-economic right that has received criticism throughout the years due to its all-encompassing breadth, with one critical aspect being that it is overly broad and as such unduly ambiguous.[9] One of the criticisms is that the broad scope makes it almost impossible for any State to fulfil the right. This is due in part to the economic ramifications of such widespread realization, but also due to the fact that, despite the greatest efforts of the most willing of States, the State can only do so much to ensure everyone's optimal health.[10] In response to this concern, there has been efforts to highlight the attributes of this right, give the normative content, and establish distinct metrics for measuring its fulfilment.[11]

General Comment 14 contains comprehensive enforcement provisions and specifies infringements to the right to health, stating that the right to health contains both freedoms and entitlements. 'These freedoms include the right to control one's health and body, including sexual and reproductive freedom, and the right to be free from interference. By contrast, the entitlements include the right to a system of health protection which provides equality of opportunity for people to enjoy the highest attainable level of health.'[12] Paragraph 9 of General Comment 14 further states that the notion of 'the highest attainable standard of health' in article 12.1 takes into account both the individual's biological and socio-economic preconditions and a State's available resources.' This paragraph acknowledges that the idea that each person has genetic, biological, and socio-economic factors that ultimately affect their health such a genetic susceptibility to the TB disease.

[8] Ibid at Art 12(2).
[9] Lawrence O Gostin, 'The Human Right to Health: A Right to the" Highest Attainable Standard of Health' (2001) 31(2) *The hastings center report* 29.
[10] Harry C Meserve, 'What Is Health?' (1963) 2(4) *Journal of Religion and Health* 263–266.
[11] Jonathan M Mann, 'Health and Human Rights' (1996) 312(7036) *British Medical Journal* 924–926.
[12] Paragraph 8

In General Comment No 3 on the nature of states parties' obligations the CESCR introduced the minimum core model for the first time. States therefore have a minimum core commitment, according to the CESCR, to ensure the fulfilment of, at the very least, the minimum essential levels of socioeconomic rights. The goal of the minimum core approach is to protect society's most vulnerable groups. The approach often entails determining subsistence levels in regard to each socioeconomic right and demanding that the provision of core goods and services enjoy immediate precedence. It consequently serves as a floor of rights that are instantly enforceable from which further realization should proceed.[13] These minimum core standards are applicable regardless of the country's resource constraints or any other challenges.[14] Under paragraph 5 of General Comment 14, the Committee acknowledges that a state's inability to fulfil obligations should not be automatically misconstrued for mere unwillingness. But rather, the Committee acknowledges that there are, in fact, tangible burdens on the State that may make it unable to fulfil its obligations. Under the Comment, a state violates its obligations if it is reluctant to use its maximum available resources for the realisation of the right to health. Furthermore, where resource constraints make compliance difficult, states have the burden of justifying that efforts were made to use all available resources at their disposal to fulfil the abovementioned commitments as a matter of priority.[15]

As such, Eleanor Kinney is of the view that General Comment 14 epitomises an important step in delineating the international human right to ICESCR member states.[16] The goal of General Comment 14 was to offer much-needed clarification on the key problems surrounding the nature of the State's obligation, which have been the subject of decades of debate. It was written to give a thorough explanation of the nature, form, and obligations that the right to health imposes on States in order to address the need for normative clarity. However, Kinney is of the view that the implementing the provisions of General Comment 14 is still challenging because of the different economic levels of the member states. It is therefore difficult to envision a mandate that would implement the right to health that is appropriate to all nations.

[13] Marius Pieterse, 'Resuscitating Socio-Economic Rights: Constitutional Entitlements to Health Care Services' (2006) 22 *South African Journal on Human Rights* 473, 481.
[14] International Commission of Jurists (ICJ), 'The Maastricht Guidelines on Violations of Economic, Social and Cultural Rights' para 9 <http://ipasa.co.za/Downloads/Patient%20Rights/Maastricht%20Guidelines%20on%20Socio-Economic%20Rights.pdf> accessed 1 November 2022.
[15] The Right to the Highest Attainable Standard of Health, U.N. Doc. E/C, Dec. 4, 2000, ICESR General Comment 14 (2000), available at *https://www.refworld.org/pdfid/4538838d0.pdf*, accessed 4 September 2019.
[16] Eleanor D Kinney, 'The International Human Right to Health: What Does This Mean for Our Nation and World?' (2001) 34 *Indiana Law Review* 1471.

It is also argued that most countries would not tolerate such excessive interference in their domestic affairs unless they have ratified the ICSECR.[17]

When the Committee's main obligations are characterized as non-derogable, especially for poorer countries, they impose an unreasonably high financial burden on them to fulfil their obligations.[18] Therefore, the minimum core is viewed as more of an effort to develop a crucial interpretive tool for assisting States in fulfilling their treaty responsibilities.[19]As a result, the General Comment tries to avoid burdening States with an overly ambitious and impossible obligations while at the same time trying to deter disingenuous inaction. This entails that despite assertions that the right to health is universal and efforts to incorporate a clear minimum standard in the General Comment, a country's health goals and economic and political circumstances frequently lead to differences in how the right is applied at domestic level. Put differently, although there is a standardized legal framework governing the right to health, the way in which it has been interpreted and ultimately realized raises concerns regarding the universality of the right.

Accordingly, there has been discussions on the potential benefits of defining the minimum core as absolute and universal in light of the huge differences in State capacity to carry out the mandate of paragraphs 43 and 44. It is argued that the nature of the minimum core makes it better suitable for international enforcement of socio-economic rights rather than for domestic enforcement. This is justified because at domestic level, the minimum core would need to be more precise, concrete, contextual, and flexible whereas the provisions of General Comment 14 provide broad guidelines for setting out the core entitlements of the populace.[20] Young similarly questions whether the minimum core should consists of a rigid, unbending set of guidelines from which no deviations are permitted.[21] She avers that insistence on the essential elements of socioeconomic rights will more likely result in agreement on only the lowest common denominator, which will more likely result in an agreement on only the bare minimum, with purposeful ambiguity. This would always have the result of making it

[17] ibid 1471–1473.
[18] Lisa Forman and others, 'What Could a Strengthened Right to Health Bring to the Post-2015 Health Development Agenda? Interrogating the Role of the Minimum Core Concept in Advancing Essential Global Health Needs' (2013) 13(1) BMC international health and human rights 1, 1–11.
[19] John Tobin, *The Right to Health in International Law* (Oxford: Oxford UP 2012).
[20] Katharine G Young, 'The Minimum Core of Economic and Social Rights: A Concept in Search of Content' [2008] *Yale Journal of International Law* 113, 135–137.
[21] ibid 113–125.

impossible to hold States accountable for any tangible substance.[22] The cumulative result of this is that the minimum core inevitably turns into a barometer that is overtly focused on how developing countries perform while yet being unable to guarantee such performance.[23] Tobin argues that the minimum core's substantive content is an unworkable list that is both nebulous and overly broad thus leaving the right to healthcare indeterminable and unclear.[24] In turn, the judiciary then faces a challenge in determining the nature and scope of State's accountability in realizing the right to health due to the lack of clarity on these issues.[25] As Müller correctly notes, we must acknowledge that international human rights do not exist in a vacuum, they are utilized in a domestic setting. These rights and corresponding obligations must therefore be read in conjunction with domestic reality.[26] International law ought to be regarded as a benchmark and democracy processes should be used to determine the nature of the claims at domestic level. This entails that people should be involved in drafting the laws that govern them, ensuring that they have a greater stake in seeing that they are more vested in ensuring their fulfilment.[27]

At a regional level, the African Charter on Human and Peoples' Rights ('the African Charter')[28] was the first regional human rights instrument to explicitly guarantee the right to health as an enforceable right. Article 16 of the Charter provides as follows:

> '1. Every individual shall have the right to enjoy the best attainable state of physical and mental health.
>
> 2. State Parties to the present Charter shall take the necessary measures to protect the health of their people and to ensure that they receive medical attention when they are sick.'

Similar to the ICESCR, the African Charter obligates States to uphold the right to health while also protecting individual health rights from unjustified interference. However, the wording of Article 16(2) has been criticised to assume a narrow interpretation of the right to healthcare.

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[22] ibid 150–172.
[23] ibid 113–140.
[24] Tobin (n 419).
[25] Lisa Forman, 'Can Core Obligations under the Right to Health Achieve Their Ambitions' (2015) 9(2) *Zeitschrift für Menschenrechte* 36–48.
[26] Amrei Müller, 'The Minimum Core Approach to the Right to Health', *Healthcare as a Human Rights Issue. Normative Profile, Conflicts and Implementation* (Transcript Verlag 2018) 55–94.
[27] ibid.
[28] 'Organization of African Unity (OAU), African Charter on Human and Peoples' Rights ("Banjul Charter"), 27 June 1981, CAB/LEG/67/3 Rev. 5, 21 I.L.M. 58' <https://www.refworld.org/docid/3ae6b3630.html> accessed 30 September 2019.

The particular reference to ensuring 'medical care to those who are sick' suggests that a State Party is only obliged to provide curative rather than preventive medical facilities for its citizens.[29] Given the prevalence of diseases of poverty[30] affecting the African region, it is a serious omission on the part of the drafters of the Charter to fail to address issues such as treatment and control of epidemics. However, one could also argue that Article 16.2 broadens the scope of the right by requiring states to take necessary steps to ensure the health of the people is protected. This would mean a wide fiat on the types of action that may be taken by a State, including exploring how human genome editing may emolliate the TB epidemic.

The African Commission on Human and Peoples' Rights ('African Commission') — a body established under the African Charter tasked with interpreting and overseeing states' adherence to their obligations under the Charter — in its 35 years of existence it has only dealt with a few cases directly or indirectly affecting the right to health.[31] Although very limited cases relating to a violation to the right to health have been brought before the Commission, the Commission has nonetheless strived to provide a purposive interpretation to the provision to the few that have been brought before it. The Commission has extended the meaning of the right to health under Article 16 to include other determinants of health.[32] Thus, 'the failure of the Government to provide basic services such as safe drinking water and electricity and the shortage of medicine ... constitutes a violation of Article 16.'[33] Based on the cases before the Commission, an inference can also be drawn that states are only obliged to provide the bare minimum of healthcare services to its people.[34] In resolution 141 of the 44th Ordinary Session, the Commission tackles the issue of access to medicine uncompromisingly. It extensively elaborates on the ambit of Article 16. In doing so, it obliges states to ensure the availability in sufficient quantities of necessary medicines and foster the development of new medicines needed for the highest attainable level of health.[35] I am of the view that by promoting

[29] Ebenezer Durojaye, 'The Approaches of the African Commission to the Right to Health under the African Charter' (2013) 13 *Law, Democracy & Development* 397.
[30] These are diseases that are more prevalent in low-income populations.
[31] The African Commission on Human and Peoples' Rights was set up a year after the African Charter came into effect on 2 November 1987 in Addis Ababa, Ethiopia and is now headquartered in Banjul, Gambia.
[32] *Sudan Human Rights Organisation and Another v Sudan* (2009) AHRLR 153 (ACHPR 2009) *(Darfur case)* paras 205, 212, 216 & 223.
[33] *Free Legal Assistance Group & Others v Zaire (*2000) AHRLR 74 (ACHPR 1995)
[34] *Social Economic Rights Action Centre and another v Nigeria* (2001) AHRLR 60 (ACHPR 2001)
[35] ACHPR/Res.141 (XXXXIIII)08: Resolution on Access to Health and Needed Medicines in Africa, available at https://www.globalhealthrights.org/instrument/achprres-141-xxxxiiii08-resolution-on-access-to-health-and-needed-medicines-in-africa-2/, accessed 1 September 2019.

development of new medicines, States are obligated to ensure the availability and accessibility of medical inventions such as gene-editing technology in the treatment of diseases.

One point of contention is the degree of immediacy with which States are required to comply with the Charter's requirements. According to certain academics, the African Charter does not provide for the progressive realization of economic, social, and cultural rights but rather they contend that these rights must be immediately realized. [36] In other words, the African Charter provides an adequate legal foundation for the prompt delivery healthcare services. However, this view has encountered opposition from other scholars who claim that, given the continent's political, social, and economic circumstances —most African States lack the material resources to enable them to enforce these rights —it would be improbable that the Charter obligations can be fulfilled immediately.[37] According to Bahar, the immediate realization of these rights is at odds with the dynamic nature of the standard of the rights.[38] He argues that the necessary preconditions for the full realization of the various socioeconomic rights are fluid since they are determined by shifting socioeconomic conditions and standards at that time. Therefore, to demand that these rights be realized immediately would entail ignoring the socio-economic realities by rushing to give effect to the rights.[39] It is therefore evident that due to the complexities, it is generally believed that the economic, social, and cultural rights in the African Charter cannot be realized immediately.[40]

III. NORMATIVE PROFILE OF THE RIGHT OF ACCESS TO HEALTHCARE

Socio-economic rights were incorporated in the Constitution in order to make the Constitution applicable to the majority of South Africans, particularly the historically disadvantaged.[41] This inclusion therefore recognizes that a fundamental obstacle to people's ability to engage fully and equally in the democratic South Africa is a lack of access to social and economic resources

[36] Chidi Anselm Odinkalu, 'Analysis of Paralysis or Paralysis by Analysis? Implementing Economic, Social, and Cultural Rights under the African Charter on Human and Peoples' Rights' (2001) 23(2) *Human Rights Quarterly* 327–340.
[37] Bahar op cit note 2 at 29.
[38] ibid 34.
[39] ibid 35–50.
[40] Matthew Craven, *The International Covenant on Economic, Social and Cultural Rights: A Perspective on Its Development* (Oxford: Clarendon 1995).
[41] Richard Goldstone, 'A South African Perspective on Social and Economic Rights' (2016) 13(2) *Human Rights Brief* 4, 4.

and services.[42] As such, the Constitution is characterised by its commitment to protecting and guaranteeing access to healthcare services for everyone. It states as follows;

> '27. (1) Everyone has the right to have access to—
>
> (a) healthcare services, including reproductive healthcare;
>
> (b) sufficient food and water; and
>
> (c) social security, including, if they are unable to support themselves and their dependants, appropriate social assistance.' [43]

The provision further obliges the state 'to take reasonable legislative and other measures, within its available resources to achieve the progressive realisation of this right.'[44] Historically, access to healthcare services in South Africa has been skewed in terms of gender, race, disability, and a number of other reasons.[45] The structures developed to provide healthcare facilities continue to inherit a disproportionate prejudice towards certain groups and diseases.[46]

Authors such as Dhai and Mohamed have even described the South African healthcare system to be in intensive care and in need of severe resuscitation.[47] Health policymakers and society at large are increasingly concerned about the need to improve access to healthcare. As a result, a plethora of projects and programs have been aimed at improving the South African healthcare system or access to it by certain groups of people.[48]

However, the key question is to what this right entitles its recipients. It is essential that the meaning of access to healthcare be accurately defined to sufficiently interpret section 27 of the Constitution. As Fried puts it, a right involves entitlements, not what they prefer to have, but what must be had and what can be demanded when needed.[49] Against this backdrop, the absence of a concrete definition makes it difficult for consumers to monitor the effectiveness of the government in meeting this right based on the available healthcare services.

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[42] Sandra Liebenberg, 'Socio-Economic Rights under a Transformative Constitution: The Role of the Academic Community and NGOs' (2007) 8(1) *ESR Review* 3, 3.
[43] The Constitution of the Republic of South Africa s 27(1)(a).
[44] ibid 27(1)(b).
[45] Karrisha Pillay, 'Tracking South Africa's Progress on Health Care Rights: Are We Any Closer to Achieving the Goal' (2003) 7 *Law, Development & Democracy* 56.
[46] ibid.
[47] A Dhai and S Mahomed, 'Healthcare in Crisis: A Shameful Disrespect of Our Constitution'' (2018) 11(1) *South African Journal of Bioethics Law* 8.
[48] LA Aday and R Andersen, 'A Framework for the Study of Access to Medical Care' (1974) 9(3) *Health Services Research* 208–209.
[49] Manitza Kotzé, 'Human Genetic Engineering in the South African Context with Its Inequalities: A Discourse on Human Rights and Human Dignity' (2014) 113(1) *Scriptura* 4.

Plaks and Butler deliberate that access to healthcare services is a complex and ill-defined issue. They state that access to healthcare consists of five interrelated factors (the 5As of access) namely; accessibility, affordability, availability, accommodation, and acceptability. This entails that healthcare services must be geographically accessible, affordable, adequately supplied (availability), and delivered so healthcare facilities meet the patient's needs and are to the patient's satisfaction (accommodation). In providing such healthcare services, the patient should also be able to communicate with a competent healthcare provider in a language with which s/he is comfortable (acceptability).[50] The issue of affordability does not function as much as a barrier to access in South Africa because healthcare services in government facilities are free for pregnant women and children up to six years and fees for the rest of the population are evaluated according to means. However, poorer communities are usually challenged with affordability and accessibility in accessing healthcare services as they cannot afford to travel long distances. Kotzé avers that poor and rural black South Africans still experience unfair access to healthcare services and the gap with their rich counterparts is ever-widening.[51]

Plaks and Butler also identify components of the accommodation aspect of access as being the most problematic.[52] Hence, the increased use of private services reflects the perception of improved quality of services in the private sector relative to accessible public services.[53] According to Marius Pieterse, inequitable enjoyment of the right of access to healthcare services can be attributed to the failure to develop the right into claimable individual entitlements, as well as the insufficient implementation of legislation measures. This has been attributed to individual entitlements and related responsibilities by government not being adequately defined.[54] Stemple contends that the absence of proper accountability on the government can be a significant barrier to progress.[55] She argues that the use of measurable benchmarks and objectives is undermined by the absence of actual implications for non-compliant governments. If no implications stem from the failure to meet legal obligations, human rights instruments become exposed to charges that they represent nothing more than empty rhetoric.[56] Mubangizi and Twinomugisha state that while countries make commitments

[50] S Plaks and MBJ Butler, 'Access to Public Healthcare in South Africa' (2012) 12 *South African Actuarial Journal* 130–131.
[51] Kotzé op cit note 49 at 2.
[52] Plaks and Butler op cit note 50 at 131–149.
[53] ibid 135.
[54] Marius Pieterse, 'Legislative and Executive Translation of the Right to Have Access to Health Care Services' (2010) 14 *Law, Democracy & Development* 20.
[55] L Stemple, 'Health and Human Rights in Today's Fight against HIV/AIDS' (2008) 22(2) *National Institutes of Health Manuscript* 10.
[56] ibid.

in the policy framework to fulfil the right of access to healthcare, they may renege on such commitments. They call for propositions to hold states accountable for infringements of the right to healthcare, and that in holding states accountable, more focus should be placed on violations as opposed to progressive realisation.[57]

Despite the government's Constitutional duty to adopt a rights-based approach in the fight against TB, questions relating to the government's level of commitment in providing healthcare services to its people by virtue of section 27 of the Constitution remain unanswered. In the fight against TB, one of the most important areas to consider is the nature of the right of access to healthcare and its legal and sociocultural implications. A veritable base from which to further study the nature of the right and its implications for right-bearers has been created by the disease's characteristics, its fatality, and the social environment in which it rapidly spreads. Legally, South Africa's healthcare commitments are drawn from two sources. The first source flows from the international commitments of the South African government, like other governments around the world, promise to undertake. Earlier in this Chapter, a discussion ensued on how international and regional instruments relating to health have elaborated on the normative content of the universal right to health as well as the binding nature of these instruments on South Africa. Section 27 of the Constitution is the second source of healthcare obligations. The relatable question to this chapter is what quality of healthcare services the Constitution seeks to guarantee to the people of South Africa. In answering this question, the semantic issues relating to the right as well as the meaning of the terms 'reasonable measures', 'available resources' and 'progressive realisation' are examined.

a) *Semantic issues relating to the 'right to have access to' compared to the 'right to'*

Notwithstanding the right of access to healthcare, healthcare services are delivered diversely. It is trite to say that section 27, like all other rights in Chapter 2 of the Constitution, must be construed in its context. As is evident later in this chapter, the language in which the right of access to healthcare is couched has made this right difficult to vindicate. The ability to identify the core of this right is therefore important, as without this, it is difficult to assess government's efforts in meeting its obligations and to challenge it where needs be. Most international instruments refer to the right to healthcare or the right to health. Mariana Buchner-Eveleigh suggests that the right to healthcare services and the right of *access* to healthcare

[57] John Mubangizi & Ben K Twinomugisha, 'The Right to Health Care in the Specific Context of Access to HIV/AIDS Medicines: What Can South Africa and Uganda Learn from Each Other?' (2010) 1 *African Human Rights Law Journal* 129.

services should not be construed to mean the same, because different implications stem from these distinct rights.[58] In this section, I argue that the right of access to healthcare services is broader in scope than the 'right to healthcare services' and it places onerous obligations on the government in fulfilling this right.

In the following analysis of the context of the right of access to healthcare services, the case of *Government of South Africa v Grootboom*[59] is discussed, in which the applicant challenged the government's housing program on the basis of section 26 of the Constitution. Like section 27, the right to have access to housing under section 26 is expressed similarly by qualifying it as a right of access. Thus, an analysis of the *Grootboom* case is useful in interpreting the right of *access* to healthcare services under section 27. Section 26 reads as follows:

> '(1) Everyone has the right to have access to adequate housing.
>
> (2) The state must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of this right.'

The court in *Grootboom* differentiated between the right to *have access to* housing under Section 26 and the right to housing under Article 11(1) of the *International Covenant on Economic, Social and Cultural Rights* (ICESCR). The Constitutional Court (CC), as per Yacoob J, noted that although international law carries considerable weight in interpreting our Constitution, the differences between the relevant provisions of the ICESCR and our Constitution are significant in determining the extent to which the provisions of the ICESCR can be of assistance in interpreting section 26.[60] The Constitutional Court (CC) noted that ICESCR provides for a right to adequate housing while section 26 provides for the right of access to adequate housing and, therefore, the right delineated in our Constitution is distinct from Article 11(1). Hence, although not expressly stated in the provision, a right of access enjoins the government to empower private organisations and all other establishments to provide such services by refraining from impairing on the right of access.[61] In projecting the

[58] Mariana Buchner-Eveleigh, 'Children's Rights of Access to Health Care Services and to Basic Health Care Services: A Critical Analysis of Case Law, Legislation and Policy' (2016) 49(2) *De Jure Law Journal* 309.
[59] *Government of South Africa v Grootboom* 2001 (1) SA 46.
[60] Ibid paras 26–28.
[61] Danwood Mzikenge Chirwa, 'Child Poverty and Children's Rights of Access to Food and Basic Nutrition in South Africa. A Contextual, Jurisprudential and Policy Analysis' 18 <https://repository.uwc.ac.za/bitstream/handle/10566/203/ChirwaChildPoverty2009.pdf?sequence=3&isAllowed=y> accessed 20 January 2020.

broader sense of a right of access, the Constitutional Court (CC) in *Grootboom* as per Yacoob J stated the following:

> 'A right of access … suggests that it is not only the state who is responsible for the provision of houses, but that other agents within our society, including individuals themselves, must be enabled by legislative and other measures to provide housing. The state must create the conditions for access to adequate housing for people at all economic levels of our society… The state's obligation to provide access … depends on context, and may differ from province to province, from city to city, from rural to urban areas and from person to person. Some may need access to land and no more; some may need access to land and building materials; some may need access to finance; some may need access to services such as water, sewage, electricity and roads.'[62]

Based on the *Grootboom* case, it is important to analyse section 27 of the Constitution through the lens of section 26. The right of access to healthcare services encapsulates the values expressed by concepts such as the right to healthcare and the right to health. This entails access to both preventive and curative healthcare services. In the search of better TB treatment methods, I suggest that the state should take cognisance of those who have been successful in their TB treatment with conventional TB drugs and those who suffer from MDR-TB. For those without MDR-TB, the government's primary obligation lies in unlocking the system by providing access to healthcare facilities to access the drugs. Those suffering from MDR-TB require more from the government subject to its available resources. Thus, section 27 enjoins the government to promote scientific research and to allow its people to benefit from scientific progress as a way of promoting the right of access. The government is obliged to create a conducive environment in which scientific research is promoted in search of advanced TB treatment or immunisation. Once that treatment or immunisation is found – which can be by using CRISPR-CasX – the government's obligation lies in making the treatment or immunisation available to the public.

However, Chirwa argues that the government's duty under section 7(2) of the Constitution – to respect, promote, protect and fulfil the rights inherent in the Bill of Rights – has made the terms 'access to' superfluous in the provision of socio-economic rights, as all these rights bring about obligations to respect, protect, fulfil, and promote. He further suggests that the Constitutional Court (CC)'s interpretation of 'access' simply encompasses some aspects of the

[62] Ibid paras 35–36.

duty to fulfil.[63] However, notwithstanding Chirwa's stance, the Constitutional Court in *Grootboom* demonstrated that in satisfying the duty to fulfil, the state should refrain from providing an umbrella form of access to healthcare services, in other words, the state should consider the needs of different categories of people. In this scenario, people suffering from MDR-TB and those with a genetic susceptibility to TB require some form of special attention and to neglect these people whose rights are in peril could be an infringement of the right.

b) Meaning of 'available resources' and 'reasonable measures'

In view of the constricted explanation of section 27, an analysis of the right of access to healthcare would be incomplete without discussing the role of the Constitutional Court in setting out the normative content of the right. Since the adoption of the Constitution, several cases have invoked the right of access to healthcare. This section analyses the South African jurisprudence to derive the interpretation of this right. More specifically, these cases are analysed to shed light on concepts such as 'available resources' and 'reasonable measures' as provided for under section 27 (2). Article 2.1 of the ICESCR reads as follows:

> 'Each State Party to the present Covenant undertakes to take steps … *to the maximum of its available resources,* with a view to achieving progressively the full realization of the rights recognized in the present Covenant by all appropriate means, including particularly the adoption of legislative measures.'

Accordingly, although General Comment 14 acknowledges that the availability of resources plays a significant role in the measures the government implements, the government must make the most of such resources. In contrast to the CESCR, which uses the wording 'to the maximum of its available resources', the South African Constitution uses the term 'within available resources', which suggests that the government's commitment does not call for more than its available resources. However, Ngwena suggests that section 27 is prone to the same criticism of vagueness directed at Article 2.1 of the ICESCR as they both fail to define the quantity or quality of healthcare services to be accessed.[64] Ngwena further argues that section 27 is, based on its wording, weaker than the ICESCR in that it refers to 'within its available' resources rather than 'the maximum of its available' resources. This suggests that the Constitutional Court should only ascertain the services the government has tried to make available, and not what services the government should have made available in the light of the resources at its

[63] Chirwa op cit note 61 at 18–19.
[64] Ngwena C, 'The Recognition of Access to Health Care as a Human Right in South Africa: Is It Enough?' (2000) 5(1) *Health and Human Rights Journal* 30.

disposal.[65] This inevitably affects the level of commitment the state should adopt in providing healthcare services.[66] According to McLean, the phrase as it is used in the South African Constitution could refer to either the resources that the state has made available or all potential resources that could be used to fulfil the state's obligations. The latter would necessitate a Constitutional Court evaluation of whether the state has made an appropriate budgetary allocation to realize the right in question.[67] Moellendorf argues that a broader sense of 'available resources' should be adopted if socio-economic rights are to guide policy rather than depend on it.[68]

The case of *Soobramoney v Minister of Health (KwaZulu-Natal)*[69] was the first opportunity for the Constitutional Court (CC) to consider the nature of socioeconomic rights and their normative content since the adoption of the new South African Constitution. The Constitutional Court was tasked with adjudicating over the issue of healthcare rationing and the right to receive emergency treatment in terms of section 27(3). The Constitutional Court opined that, given the socio-historical context of South Africa, the lack of resources available to the State was a constraint on Mr Soobramoney's enjoyment of the right. In this case, Mr Soobramoney suffered from chronic renal failure which necessitated renal dialysis. He had been receiving such care from the Addington State Hospital's renal unit in Durban. His condition worsened and his life could only be prolonged through regular renal dialysis but due to limited facilities, the hospital was unable to provide the treatment he had requested. In this regard, the applicant lodged an application to compel Addington Hospital to provide the necessary treatment for him by virtue of section 27(3) of the Constitution.[70] The implication of the applicant's case was to enjoin the state to re-allocate resources to meet his healthcare needs.

The Constitutional Court held that the right to healthcare services cannot be construed outside of the context of the availability of health services generally. The Constitutional Court further held that 'it would be substantially difficult for the State to fulfil its primary responsibility under section 27(1) and (2) to provide healthcare services to 'everyone'. In view of that, the Constitutional Court (CC) stated that 'the diversion of additional resources

[65] Darrel Moellendorf, 'Reasoning about Resources: Soobramoney and the Future of Socio-Economic Rights Claims Cases and Comments' (1998) 14(2) *South African Journal on Human Rights* 327–333.
[66] Ngwena op cit note 64 at 31.
[67] Kirsty McLean, *Constitutional Deference, Courts and Socio-Economic Rights in South Africa* (Pretoria University Law Press 2009) 195.
[68] Moellendorf op cit note 65 at 332.
[69] *Soobramoney v Minister of Health* (1998) (1) SA 765 (CC).
[70] It provides that no one may be refused emergency medical treatment.

to the renal dialysis programme would prejudice other important health programmes[71] as well as the resources available to the State to meet other socio-economic needs such as housing, food, water, and social security.'[72] The Constitutional Court was not convinced that it was reasonable to require the state to allocate additional resources to the renal dialysis program for all patients. This demonstrates that attaining equitable access to health services in South Africa remains to be realised. As such, the Constitutional Court held that the decision to limit access to dialysis in such circumstances was rational and that 'a court will be slow to interfere with rational decisions taken in good faith by the political organs and medical authorities whose responsibility it is to deal with such matters.'[73] In addition, the applicant had no cause of action in terms of section 27(3) of the Constitution but rather the applicant's claim fell within the ambit of sections 27(1) and (2) of the Constitution.[74] In *Van Biljon v Minister of Correctional Services,*[75] the court clarified the quality of healthcare to which prisoners are entitled. The court held that the Constitution did not give prisoners the right to the best medical treatment but only that which is adequate. The meaning of adequate medical treatment must be linked to what the state can afford to treat.

Accordingly, the Constitutional Court has devised a methodology of reasonableness review to assess the positive obligations imposed by the socio-economic right. The main inquiry of the Constitutional Court is whether the means adopted are reasonably capable of aiding the realization of the socio-economic rights in question.[76] As such, the Constitutional Court (CC) in *Grootboom* ventured on an exercise to define the parameters of what constitutes 'reasonable measures.' In consequence, the Constitutional Court set standards to assess whether a government programme has been reasonably implemented to realise the socio-economic right. The Constitutional Court noted that the key criteria for a reasonable program or policy is that it must be thorough, coordinated, transparent, and have its contents adequately communicated to the public. Most importantly, the programme in question must cater for those in urgent need.[77]

[71] Ibid paras 27–28.
[72] ibid 19.
[73] ibid 29.
[74] Ibid para 22.
[75] *Van Biljon v Minister of Correctional Services* 1997 (4) SA 441.
[76] Sandra Liebenberg, 'Basic Rights Claims - How Responsive Is "Reasonableness Review"?' (2004) 5(5) *ESR Review* 8.
[77] ibid 8–9.

The Constitutional Court insisted that in assessing the government's duty to fulfil its constitutional obligation, the concept of reasonableness means more than a mere assessment of simple progress made but rather evidence has to be provided to prove that sufficient attention has been paid to the particular need.[78] According to the Constitutional Court, reasonable measures had to be determined because the Constitution created different arms of government and assigned different functions between these arms with the aim that they cooperate in carrying out their constitutional tasks.[79] The Constitutional Court opined, nevertheless, that it was unreasonable to take measures that do not address the needs of those whose ability to enjoy the right are in peril.[80] Implementing strategies that were not 'reasonable' would not comply with the state's obligations under section 27(2) of the Constitution. Our Constitutional Court therefore applies the reasonableness approach in finding if a government's programme is unreasonable in failing to provide for those in desperate need in the short term.[81] Despite not endorsing the minimum core obligations approach of the CESCR, the reasonableness approach avoids the legitimacy and competence objections to the justiciability of socioeconomic rights because it involves the Constitutional Court scrutinizing programs and policies of the government, without mandating solutions or pre-eminent policy decisions by the executive and legislative branches.[82] The reasonableness approach was hence applied in the *Mazibuko v City of Johannesburg*[83] case where the Constitutional Court stated that it will be reasonable for municipalities and provinces to strive first to achieve the prescribed minimum standard before proceeding to provide beyond this standard for those to whom the minimum has already being provided.[84]

In *Grootboom*, the Constitutional Court (CC) further stated that the measures adopted must be reasonably implemented. This raises the critical issue of what constitutes reasonable implementation. I suggest that the 'reasonable implementation' the government is expected to undertake to achieve the right of access to healthcare services is a matter of interpretation. The capacity of the institutions in charge of implementing health policy as well as the social, economic, and historical context is taken into consideration while determining

[78] *Government of South Africa v Grootboom* at para 44.
[79] Ibid para 39.
[80] Ibid para 44.
[81] Sisay Yeshanew, 'Combining the "Minimum Core" and "Reasonableness" Models of Reviewing Socio-Economic Rights' (2008) 9(3) *ESR Review* 9.
[82] ibid 10.
[83] *Mazibuko v City of Johannesburg* 2010 (3) BCLR 239 (CC).
[84] ibid 76.

reasonableness.[85] Pillay also suggests that reasonable implementation must be understood as reflecting on the results and to what degree the interventions achieve the goals proposed.[86] Thus, to determine whether there has been such 'reasonable implementation', consideration needs to be given towards the levels of implementation of national health legislation, access to health facilities, implementation of primary level healthcare services, access to drugs, and quality of healthcare services. The level of scrutiny used by the Constitutional Court (CC) therefore goes beyond just determining whether the policy was logically thought out and implemented in good faith.

Worryingly, the Constitutional Court has not substantively clarified the normative content of the right and there is a vacuum in the interpretation of the quality of healthcare services to which South Africans are entitled. Unlike the CESCR, the Constitutional Court of South Africa has been reluctant to recognise minimum core obligations as a self-standing right conferred on everyone due to the diversity of people's needs and their differing contexts. The Constitutional Court in *Grootboom* declared that 'it is not possible to determine a minimum threshold for the progressive realisation of the right to adequate housing without first identifying the needs and opportunities for the enjoyment of such a right'[87] The Constitutional Court noted that this challenge is made more difficult by the fact that groups are positioned differently and have diverse social demands. Although the Constitutional Court in the *Minister of Health v Treatment Action Campaign*[88] did not expressly reject the minimum core, it did rule that the socio-economic rights outlined in the Constitution should not be interpreted to give everyone the right to demand that the minimum core be provided to them, without taking into account progressive realization and resource availability. It further stated that it is difficult to provide everyone with access to even a core service right away and that the only thing that can be expected of the state is that it acts properly to offer access to socioeconomic rights gradually.[89] In this case, the Constitutional Court considered the reasonableness of a government policy in facilitating access to antiretroviral treatment to prevent mother-to-child transmission of HIV. The Constitutional Court noted that the essential elements of the definition of healthcare services must be considered in assessing whether a programme constitutes a coherent one. In the *Mazibuko* case, the Constitutional Court once more refrained from establishing a minimum

[85] Liebenberg, 'Basic Rights Claims - How Responsive Is "Reasonableness Review"?' (2004) 5 *ESR* 9.
[86] Pillay op cit note 45 at 45.
[87] *Government of South Africa v Grootboom* at para 32.
[88] *Minister of Health v Treatment Action Campaign* (2002) 5 SA 721 (CC).
[89] ibid 35.

core requirement for the right to obtain water on the grounds that, among other things, 'what the right requires will vary over time and in context.'[90]

However, even if the Constitutional Court (CC) believes it may not be practicable to provide everyone with access to a fundamental service right away, the state must make sure that at the very least a sizable percentage of population have access in order to conform to the CESCR's interpretation in General Comment No. 3 of the states obligations in relation to socio-economic rights. What is also important to note is that the Constitutional Court has not expressly rejected the minimum core idea. The Constitutional Court accepted that 'there may be cases where it may be possible and appropriate to have regard to the content of a minimum core obligation to determine whether the measures taken by the State are reasonable.'[91] In addition, the Constitutional Court's hesitation to endorse the concept was also founded on worries about structural and democratic concerns.[92] The Constitutional Court considered itself ill-equipped to establish what the minimal core requirements are. In *Treatment Action Campaign* the Constitutional Court stated that courts are ill-equipped to decide cases where the community can suffer many social and economic repercussions from Constitutional Court judgments. The Constitution envisions a relatively limited and narrow role for the Constitutional Court, namely, to order the state to take actions to fulfil its constitutional commitments and to assess whether these actions are reasonable. The judicial, legislative, and executive branches of government attain the proper constitutional balance in this way.[93] Essentially, the Constitutional Court itself affirmed that so long as an executive action impacts on the protection and fulfilment of fundamental rights, the doctrine of separation of powers cannot be demarcated using fixed parameters.[94]

Furthermore, as witnessed in the *Soobramoney* case, the Constitutional Court is reluctant to exert supervisory powers over the government in terms of socio-economic rights. The efficacy of section 27 as a judicial instrument for fostering improved healthcare services will depend in part on the judiciary's ability and willingness to investigate alleged breaches of socio-economic obligations by the state.[95] From the judgments discussed above, it is

[90] *Mazibuko v City of Johannesburg* at para 60.
[91] *Government of South Africa v Grootboom* ar para 33.
[92] *Minister of Health v Treatment Action Campaign* at para 38. See also *Mazibuko*, para 61.
[93] ibid.
[94] ibid 98.
[95] Ngwena op cit note 64 at 31.

difficult to use the Constitutional Court to challenge a specific allocation of healthcare resources. While it is often argued that judicial encroachment of the state's obligation to enforce socio-economic rights might distort the functioning of the doctrine of separation of powers and lead to serious financial implications (as held by Chaskalson CJ in the *Soobramoney* case), I suggest that the financial and budgetary implications should not compromise the justiciability of the right of access to healthcare services. Because of exercising this caution, the Constitutional Court has been unable to succinctly set out the normative content of the right of access to healthcare. The Constitutional Court (CC) in *Soobramoney* should not have shied away from its constitutional obligation to sufficiently inquire into budget appropriations. Liebenberg suggests that the failure to develop the normative content of the right, including its relationship with other rights such as the right to life — as the Constitutional Court declined to do in *Soobramoney*[96] — results in a disproportionate emphasis on the State's justificatory claims.[97]

According to Chapman, violations of the right of access to healthcare may take three forms; these entail violations arising from actions and policies of the government; violations linked to patterns of discrimination; and violations linked to inability to fulfil the minimum core obligations.[98] As stated in paragraph 43 of General Comment 14,within the obligations to respect that forms part of the minimum core is making sure there is no discrimination of any kind in the delivery of the right. In the *Treatment Action Campaign* case it was held that:

> 'The state is obliged to take reasonable measures progressively to eliminate or reduce the large areas of severe deprivation that afflicts our society. The s will guarantee that the democratic processes are protected to ensure accountability, responsiveness and openness, as the Constitution requires in its section 1. As the Bill of Rights indicates, their function in respect of socio-economic rights is directed towards ensuring that legislative and other measures taken by the state are reasonable.'[99]

As such, the Constitutional Court upheld the decision that the government's policy was inconsistent with sections 27(1) and (2) of the Constitution. It held that the government had not reasonably addressed the need to reduce the transmission of HIV from mother to child by not making Nevirapine available in all public clinics and hospitals, which at the time was available

[96] *Soobramoney v Minister of Health* at paras 15–19.
[97] S Liebenberg, *Socio-Economic Rights: Adjudication under a Transformative Constitution* (2010) 146.
[98] AR Chapman, 'A Violations Approach to Monitoring Economic, Social and Cultural Rights' (1996) 18 *Human Rights Quarterly* 23–66.
[99] *Minister of Health v Treatment Action Campaign* at para 36.

only at 18 research sites. The Constitutional Court noted that in assessing reasonable measures 'such determinations may in fact have budgetary implications but are not in themselves directed at rearranging budgets.'[100] Hence, the Constitutional Court considered, among other things, the effects of the roll-out on limited resources and the related budgetary consequences. The Constitutional Court stated that although its orders to enforce claims for socio-economic rights may have budgetary ramifications, they are not 'in themselves directed at reordering budgets.'[101]

An analysis of the judgments suggests that the right of access to healthcare services is vulnerable to cultural, political, economic, linguistic, and legal problems. I suggest that while the economic and legal problems can be solved in due course, the language in which the right is proclaimed remains a major problem. Language plays a fundamental role in explaining the level of government obligations. Sprumont, for example, argues that 'as long as the content of the right to healthcare cannot be explained substantively, the obligations imposed on the state remain more political than legal.'[102] First, the issue of available resources serves as the apex of the quality of healthcare services that the government can provide. One would therefore argue that providing healthcare services in South Africa has assumed the role of 'charitable work' whereby the government only makes available that which it can afford and not to what the people are entitled. Rationing policies in the health sector exacerbate inequality in access to healthcare but, as in the case of *Soobramoney*, it seems inevitable due to limited resources.[103] Although the goals must be balanced with measures adopted by the state, the availability of resources is an important factor in determining what is reasonable.[104] Rationing is essential in determining who gets to access the 'available limited resources.' Chaskalson CJ stated the following in the *Soobramoney* case:

> 'What is apparent from this provision is that the obligations imposed on the state by section 27 in regard to access to … healthcare … is dependent upon the resources available for such purpose, and that the corresponding right themselves are limited by reason of the lack of resources. Given this lack of resources and the significant demands on them that have already

[100] Ibid para 38.
[101] ibid.
[102] Dominique Sprumont, 'The Unwritten Constitutional Right to Subsistence Brief Comment of 27 October 1995 Judgment of the Swiss Federal Court in the Perspective of a Right to Health Care' (1998) 5(4) *European Journal of Health Law* 414.
[103] Ebi Achigbe Okeng Ebi *Enforcing the Right of Access to Healthcare Services in South Africa* (unpublished LLM thesis, University of South Africa, 2016) 29.
[104] *Government of South Africa v Grootboom* at para 46.

been referred to, an unqualified obligation to meet these needs would not presently be capable of being fulfilled.'[105]

However, as held in the *Grootboom* case, when rationing the healthcare services, priority should be given to vulnerable members of the society for it to be considered reasonable. Hence, the terms 'reasonable measures' and 'available resources' avoid outlining a comprehensive list of policies and healthcare services that the government must offer. As a result, it is envisaged that the reasonable measures will always be evaluated as circumstances and the populace's current health challenges demand. Liebenberg suggests strengthening the Constitutional Court (CC)'s review standards by including a more vigorous proportionality analysis. The stronger proportionality analysis would necessitate that the government must demonstrate that there are no less restricting ways to do other than preventing access to the socio-economic right in question.[106] Hence even if the government can present a convincing argument that it is impractical to provide everyone a minimal level of service, it must also demonstrate that another lesser type of restriction was considered.[107]

c) Progressive realisation

The socioeconomic rights mentioned in Section 27 obligates the government to take reasonable legislative and other measures to 'progressively realize' these rights. This is quite similar to Article 12 of the ICESCR which provides that State parties shall take steps to achieve the realisation of the right to health. The term progressive realisation has been defined by the ICESCR. The ICESCR stated as follows:

'The concept of progressive realization constitutes a recognition of the fact that full realization of all economic, social and cultural rights will generally not be able to be achieved in a short period of time. In this sense the obligation differs significantly from that contained in article 2 of the International Covenant on Civil and Political Rights which embodies an immediate obligation to respect and ensure all of the relevant rights … It is on the one hand a necessary flexibility device, reflecting the realities of the real world and the difficulties involved for any country in ensuring full realization of economic, social and cultural rights. On the other hand, the phrase must be read in the light of the overall objective, indeed the raison d'être, of the Covenant which is to establish clear obligations for States parties in respect of the full

[105] *Soobramoney v Minister of Health* at para 19.
[106] Liebenberg op cit note 85 at10.
[107] ibid.

> realization of the rights in question. It thus imposes an obligation to move as expeditiously and effectively as possible towards that goal … .'[108]

The obligation to progressively realize the right to health over time under the ICESCR implies that States are subject to specific, continuous obligations that call for urgent action and consideration of the most efficient path to the achievement of their health objectives.[109] Accordingly, in an attempt to achieve these health objectives States must be conscious of their tripartite obligations — to protect, respect and fulfil. A substantial of the work necessary in progressive realization of the right to health is related to the obligation to fulfil. According to paragraph 33 of General Comment 14, the obligation to *fulfil* requires States to adopt appropriate legislative, administrative, budgetary, judicial, promotional and other measures towards the full realization of the right to health.[110] Put differently, the obligation to fulfil contains obligations to facilitate, provide and promote. This entails that the progressive realization of the right of access to healthcare must be evident in its implementation — explicitly stated in legislative action, clearly set in administrative action and included in budgetary allocations. Dingake agrees that a human rights-based approach is a prerequisite for the efficient treatment of TB. He avers that no significant progress can be accomplished without putting the right of access to healthcare at the core.[111] Hence, with a rights-based approach, the government as duty bearers must fulfil this right in the treatment of TB and account for failure to do so. If a health plan is set out, the approach for executing it must be detailed with a clear goal in mind for the progressive realization of health as well as an indication of a timeframe to realise the plan. For instance, in 2014, the WHO introduced the 'End TB Strategy' which provided a paradigm shift towards TB elimination by embracing human rights as the main pillar for prevention and care of TB.[112] The End TB strategy not only gives a precise estimate of the financial resources required to end TB and a design of the necessary priority activities, it also clearly sets a time frame — 2030 — by which TB as a public health should have been eradicated.

[108] CESCR, General Comment No. 3 para 9.
[109] 'General Comment No. 14, E/C.12/2000/4 (2000)' at para 31.
[110] 'General Comment No. 14, E/C.12/2000/4 (2000)' (n 239).
[111] OBK Dingake, 'Human Rights, TB, Legislation, and Jurisprudence' (2017) 19(1) *Health and Human Rights* Journal 305–306.
[112] See https://www.who.int/tb/End_TB_brochure.pdf?ua=1, accessed 26 September 2019.

Furthermore, to give impact to this duty, Dingake proposes the need to legislate on TB whether specifically or as part of the right of access to healthcare so that there is little room for guesswork when it comes to enforcing the rights of TB patients.[113] Fahy notes that this rights-based approach requires identifying the importance of defending the rights of individuals who are susceptible to TB and those with TB, especially in terms of preventing the spread of the disease and ensuring quality therapy is available and accessible to all.[114] Gianella et al argue that adopting a human rights approach encompasses being responsive to structural and genetic variables that increase people's exposure to TB, restrict access to quality health facilities, and make individuals more susceptible to TB infection.[115] The term 'progressive' realisation by its very nature indicates that the steps taken by the government to achieve its health goals must be proactive and not a retrogression on progress already made. Paragraph 32 of General Comment 14 is clear that retrogressive measures in relation to the right to health are not permissible. If any intentionally regressive actions are taken, it is the State party's responsibility to demonstrate that they were implemented after carefully weighing all available options and that they are appropriately justified in light of all the rights guaranteed by the Covenant. Liebenberg avers that retrogression is permissible when it is aimed at achieving equity and correcting of structural imbalances and that the steps taken are not particularly averse to the disadvantaged and marginalized.[116]

The definition of progressive realisation provided by the CESCR has also been endorsed by the Constitutional Court of South Africa. The Constitutional Court in the *Grootboom* case that the term bears the same meaning in the South African Constitution. The Constitutional Court (CC) stated as follows

> 'Although the committee's analysis is intended to explain the scope of states parties' obligations under the Covenant, it is also helpful in plumbing the meaning of 'progressive realisation' in the context of our Constitution. The meaning ascribed to the phrase is in harmony with the context in which the phrase is used in our Constitution and there is no reason

[113] Dingake op cit note 111 at 307.
[114] S Fahy, 'Rights-Based TB Programs for Migrants and Prisoners Needed in North Korea' (2016) 18(1) *Health and Human Rights Journal* 110.
[115] C Gianella, MA Pesantes, C Ugarte-Gil et al 'Vulnerable Populations and the Right to Health: Lessons from the Peruvian Amazon around Tuberculosis Control' (2019) 28(18) *International Journal for Equity in Health* 1–2.
[116] Liebenberg op cit note 97.

not to accept that it bears the same meaning in the Constitution as in the document from which it was so clearly derived.'[117]

In the *Grootboom* case, the Constitutional Court (CC) further noted that, in line with the CESCR, the word progressive realisation meant that the right of access does not have to be instantly realised but rather the government must take action to fulfil the Constitution's mandate that the basic requirements of all persons in our society be efficiently satisfied. Progressive realization places a responsibility on the state to enhance the nature and quality of the services to which people have access, even where people already have access to socio-economic rights.[118] It is therefore clear from the explanation of the concepts of the available resources, reasonable measures and progressive realisation that the right of access to healthcare services must be concrete, clear and with steps of progressive realisation. In the case of *Mazibuko v City of Johannesburg*,[119] 'the idea of progressive realisation recognises that policies developed by the state will need to be evaluated and updated to guarantee that the realisation of social and economic rights is progressively realized'.[120] The Constitutional Court therefore found that the need to ensure the progressive realisation of rights was consistent with the adjustment of policies over time. Bilchitz sheds light on the connection between the minimum core and progressive realization, noting that states are required to instantly realize a minimum level of provision for a right and then to gradually raise that level above the minimum.[121] He clarifies that progressive realization acknowledges 'what government is required to do is to provide core services to everyone without delay that will meet their survival needs and then qualitatively to increase these services so as ultimately to meet the maximal interests that the state is required to protect'.[122] This approach is consistent with how the CESCR views progressive realisation, which it defines as involving the provision of the bare minimal standards of a right, which a state is then obliged to enhance over time. Hence, if current TB policies or campaigns are not sufficiently efficient in emolliating TB, the government is duty bound to incorporate other policies that seek alternative forms of treatment such as heritable human genome editing. This must also be coupled with deliberate and quantifiable government action that is subject to structures of accountability.

[117] *Government of South Africa v Grootboom* at para 45.
[118] Liebenberg at op cit note 97 at 188.
[119] *Mazibuko v City of Johannesburg*.
[120] ibid 40 & 67.
[121] D Biltchz, 'Towards a Reasonable Approach to The Minimum Core: Laying the Foundations for Future Socio-Economic Rights Jurisprudence' [2003] *SAJHR* 11.
[122] ibid 12.

That being the case, if the right of access to healthcare services is violated and for which no justification can be found, is the right of access to healthcare services justiciable? The justiciability of the right of access to healthcare should be understood to mean whether the aforementioned right can be subject to review by a judicial or a quasi-judicial body.[123] Although the term 'enforceability' is normally used as a synonym for justiciability, Arambulo distinguishes between the two terms by submitting that justiciability applies to the question of whether the right is open to interpretation by a judicial or quasi-judicial body and, thus, whether a complaint may be lodged with that body concerning the alleged violation. Conversely, enforceability is larger in scope and entails that a judicial or quasi-judicial body's judgment on a specific human right can be effectively enforced and implemented, for example, through specific remedies.[124] Chirwa suggests that the right to health and the obligation to provide (access to) healthcare services is capable of being justiciable both directly and indirectly through other rights.[125] Nonetheless, recognising the right of access to healthcare as a stand-alone justiciable right under section 27 is a step in the right direction as it allows for the proper development of its content and the specific duties on the state.

IV. BRINGING GENE-EDITING TECHNOLOGY TO THE PEOPLE

The right of access to healthcare services is an empty promise if there is no practical access such services. The WHO has defined 'access' as the equitable availability and affordability of essential medicines.[126] The right of access to healthcare services imposes tripartite obligations on government.[127] These healthcare obligations have been derived from international healthcare commitments that the South African government, like other governments in the world, has promised to undertake as well as the Constitutional Court 's interpretation of socio-economic rights. Bilchitz distinguishes between positive and negative obligations. He summarises the obligations as follows:

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[123] Maitetxu San Giorgi, *The Human Right to Equal Access to Health Care* (published PhD thesis, Erasmus University Rotterdam, 2012) 79.
[124] ibid 80.
[125] Danwood Mzikenge Chirwa, 'The Right to Health in International Law: Its Implications for the Obligations of State and Non-State Actors in Ensuring Access to Essential Medicine' (2003) 19 *SAJHR* 558.
[126] Katrina Perehudoffa, 'Universal Access to Essential Medicines as Part of the Right to Health: A Cross-National Comparison of National Laws, Medicines Policies, and Health System Indicators' (2020) 13(1) *Global Health Action 2.*
[127] Ebi Achigbe Okeng Ebi, *Enforcing the Right of Access to Healthcare Services in South Africa* (unpublished LLM thesis, University of South Africa, 2016) 21.

> '[A] negative obligation consists in having a duty not to interfere with the ability of someone to do something they are entitled to do; a positive obligation, on the other hand, requires one to act in a particular way to provide something for someone.'[128]

While negative obligations can be enforced instantly, the positive obligations imposed on the government do not provide an automatic entitlement to access the healthcare service in question.[129] Heyns and Brand assert that the right of 'access' does not oblige the government to offer the product in question (food as per their example) but rather it enjoins the government to ensure that the product is reasonably accessible and inexpensive.[130] In exploring the state obligations that follow from the right of access to healthcare services, it will become evident that the obligations to respect, protect and fulfil overlap to a certain extend. This has, in practice, led to great difficulties in separating the different obligations as different measures taken to comply with the obligations can overlap across the obligations.[131] Most importantly, this has also highlighted the interdependence of duties — that the right of access to healthcare services can only be fully realised by fulfilling all three obligations.[132] In the following, I discuss the obligations to protect, respect, and fulfil. Thereafter, I outline a case for why access to gene-editing technology such as CRISPR for the treatment of TB falls within the right of access to healthcare services.

a) Obligations to respect

This is a negative obligation which calls for the government not to unnecessarily interfere in the enjoyment of the right (directly or indirectly).[133] This bestows a duty not to unnecessarily restrict biomedical research and not to unnecessarily interfere in society's efforts to access gene-editing technology.[134] It implies that the government has the duty to honour the freedoms and autonomy of the people.[135] Hence, to deny people access to CRISPR TB preventative or

[128] D Biltchz, 'Towards a Reasonable Approach to The Minimum Core: Laying the Foundations for Future Socio-Economic Rights Jurisprudence' (2003) *SAJHR* 7.
[129] Michelle du Toit, *An Evaluation of the National Health Insurance Scheme in the Light of South Africa's Constitutional and International Law Obligations Imposed by the Right to Health* (unpublished LLM thesis, Stellenbosch University, 2017) 37.
[130] C Heyns & B Brand, 'Introduction to Socio-Economic Rights in the South Africa Constitution' (1998) *Law, Development and Democracy* 158.
[131] Maitetxu San Giorgi, *The Human Right to Equal Access to Health Care* (Unpublished PhD thesis, Erasmus University Rotterdam, 2012) 50.
[132] ibid 49.
[133] Ximena Andión Ibañez & Tamar Dekanosidze, 'The State's Obligation to Regulate and Monitor Private Health Care Facilities: The Alyne Da Silva Pimentel and the Dzebniauri Cases' *Public Health Reviews* 3.
[134] ibid.
[135] Shelton Tapiwa Mota Makore, *Expanding Access to Essential Medicines through the Right to Health: A Case Study of South Africa* (Unpublished Master of Laws, University of Fort Hare, 2015) 36.

curative therapies could be infringing on this obligation. It also bestows the duty not to withhold or distort knowledge that is valuable in treating TB.

b) Obligation to protect

The duty to protect entails that states are obliged to ensure that third parties do not unnecessarily restrict people's access to certain forms of treatment. The state is further implored, *inter alia*, to control the pricing of pharmaceuticals and to ensure that vulnerable groups are be given special attention.[136]

c) Obligation to fulfil

The obligation to fulfil relates to the constructive measures taken by the government to ensure the right of access to healthcare is realised. This obligation calls for steps that 'create, maintain and restore' the health and wellbeing of the people. Accordingly, it enjoins the government to take steps to ensure the protection of the right through legislative, budgetary, and administrative measures. The Constitutional Court (CC) in *Grootboom* demonstrated that in satisfying the duty to fulfil, the state should refrain from providing an umbrella form of access to healthcare services but should rather consider the needs of different categories of people. This duty therefore requires the government to take positive measures in assisting certain groups of people or the society at large in enjoying their right and requires the government to provide accurate information about the healthcare system to enable the public to realize their rights and make informed decisions regarding their choice of healthcare services.[137] Generally, adherence to the obligations relating to socio-economic rights depends on the availability of resources. While the Constitutional right of access to healthcare services for everyone may indicate equality of access, the prioritisation of scarce medical resources is nothing new in South Africa.[138] No country can ever fully satisfy demand for its health services. While human genome editing raises a number of challenges, the issue of affordability looms the highest in the payers' and decision-makers' minds.[139]

Although most CRISPR therapies are still in the clinical trials stage, the few gene therapy products that have gained clinical application illustrate the anticipated high price tag that may

[136] ibid 37.
[137] du Toit op cit note 129 at 39.
[138] Keymanthri Moodley & Theresa Rossouw, 'What Could Fair Allocation of an Efficacious COVID-19 Vaccine Look like in South Africa?' (2020) *The Lancet Global Health* 1.
[139] Grace Hampson and others, 'Gene Therapy: Evidence, Value and Affordability in the US Health Care System' (2017) 7(1) *Journal of Comparative Effectiveness Research* 18.

be attached to germline editing. [140] Human genome editing treatments currently costs between $373,000 and $2.1 million[141] which locally translates to R5 439 190.44 and R30 622 788.00 respectively. Conceptually, it is simpler to answer the question of a long-lasting, possible curative medical intervention versus a lifetime of suffering from TB and/or a life cut short. However, in practice, those entrusted in making these therapies accessible to the people are faced with a number of dilemmas.

The development of CRISPR therapeutics will most likely cause the conventional biopharmaceutical business model to change fundamentally.[142] This is because conventional TB drugs are aimed at slowly killing the bacteria over a period — several months — whereas CRISPR therapies on the other hand alter the disease treatment process with usually a once off treatment regime. This essentially means that unlike the conventional pharma models which are based on patients taking medications over an extended period thus making them considerably cheaper (per unit cost), treating TB using CRISPR therapies will incur a heavy frontloaded charge making the cost per unit to be much higher.[143] As a result, the South African healthcare system will be confronted with the burden of absorbing high upfront costs.

There is little value in a treatment that is inaccessible to people who need it the most. A treatment method that is unavailable to the masses has no value at all. Regarding eradicating the TB epidemic in South Africa, the benefit of human genome editing can only be understood once the masses have access to its transformative and lifetime effects. The South African healthcare system is already under strain and the current cost of managing drug-resistant TB, for instance, needs to be assessed against that of a possibly expensive single therapeutic cure. Accordingly, if the South African health budget is not stretched a little to ensure gene editing is available to everyone, the anticipated high costs of gene editing re-opens a door to old injustices where gene-editing therapies will only be available to the few who can afford private healthcare. As already stated, the obligation to fulfil enjoins the government to take steps to take legislative and budgetary measures to ensure that gene editing services are available to

[140] Laura Hercher & Anya ER Prince, 'Gene Therapy 's Field of Dreams: If You Build It, Will We Pay?' (2019) 97(5) *North Carolina Law Review* 1471.
[141] Anne WT Muigai, 'Expanding Global Access to Genetic Therapies' (2022) 40 (21–22) *Nature Biotechnology* 20.
[142] Sanjay Srivastava, 'How Cell and Gene Therapy is Transforming Healthcare' [2020] *Cell & Gene* <https://www.cellandgene.com/doc/how-cell-and-gene-therapy-is-transforming-healthcare-0001> accessed 6 August 2020.
[143] Jakub P Hlávka, *Three Essays in Health Economics: Towards Alternative Payment Models for High-Value, High-Cost Medical Treatments* (Unpublished PhD thesis, University of Southern California, 2018) 5.

everyone. The duty to protect equally compels the government to take positive measures to assist the groups of people or the society who cannot afford gene-editing services.

With this in mind, it is difficult to comprehend how the government will absorb these high costs for all its public health users. The emergence of CRISPR therapies therefore raises concerns and controversies about fairness and distributive justice across the different layers of society. To this end, an ethical question to be asked is how CRISPR therapies for the treatment of TB can be made available to all members of society despite being available in limited quantities.

Implicit in these obligations is also the recognition that the realisation of the right of access to healthcare services and its usefulness in contributing to the enjoyment of other human rights broadly embodies three interrelated dimensions: accessibility, availability, and quality. Expecting access to gene-editing technology under the right should therefore encompass all these dimensions. When exploring whether middle-income countries like South Africa and their citizens will benefit from this new technology within the ambit of the right of access to healthcare services, questions of affordability and how stringent potential clinical applications of CRISPR should be regulated are worth addressing.[144] The dawn of human genome editing (now) is a ripe time to consider such issues.

V. PRIORITY SETTING AND RATIONING FOR GENE EDITING SERVICES

Heritable genome editing may very well turn out to be a crucial weapon in South Africa's fight against the deadly and enduring TB epidemic as it could develop into a genetic vaccine.[145] It is therefore important to consider whether heritable genome editing can ever be applied widely, much like a vaccination. Thaldar et al aver in order for this to be possible, the editing of embryos needs to be liberated from the IVF laboratory through a minimally invasive or, ideally, non-invasive operation.[146] As discussed in chapter 1, there are a number of CRISPR delivery methods that can be explored such as *in utero* and/or *in vivo* to deliver CRISPR therapies. More so, a number of preclinical studies have been conducted in diverse animal models — mice, rats

[144] King NMP, 'Human Gene-Editing Research: Is the Future Here Yet?' (2019) 97(5) *North Carolina Law Review* 1070.
[145] Donrich Thaldar, Bonginkosi Shozi and Tamanda Agatha Kamwendo, 'Culture and Context: Why the Global Discourse on Heritable Genome Editing Should Be Broadened from the South African Perspective' (2021) 4 *BioLawJournal –Rivista di BioDiritto* 415.
[146] ibid at 415.

and sheep[147]— in respect of in utero therapeutic applications of gene therapy. However, considering that initial CRISPR therapies may be available in limited quantities, is the thought of using the mass rollout of non-invasive in utero heritable genome editing to prevent contracting TB far-fetched?[148]

Although used interchangeably, rationing and priority setting in a healthcare setting are two distinct concepts. They are however aimed at serving the same purpose — distributing scarce healthcare resources among competing users. Rationing refers to the distributing of medical resources where such resources are limited by circumstances and thus entails 'withholding potentially beneficial treatments from some individuals.'[149] In contrast, priority setting in healthcare settings refers to the process by which the government prioritises certain healthcare services or categories of patients to receive such services.[150]

Authors have sought to draw a clear distinction between the two concepts by arguing that rationing has a negative connotation to it. It is argued that rationing is strongly associated with an element of scarcity and coerced decision making by the government.[151] To the contrary, priority setting may be understood as a method implored by government and one that is consciously achieved — based on well-defined rules and criteria.[152] Priority setting therefore indicates a situation of being in control driven by the desire to make use the medical resources more efficiently.

Priority setting in this current study would revolve over the issues of who should have access to gene editing services first? What criteria will the government implore in deciding how to distribute the limited CRISPR therapies? In deciding the above, it would be unrealistic to argue that no government has ever allocated 'enough' healthcare resources.[153] Accordingly, most healthcare systems, including that of South Africa have in one way or the other practiced the rationing of healthcare services. Priority setting therefore calls upon the government to decide on which category of citizens to prioritise for TB treatment using CRISPR. While

[147] See S Nakamura, S watanabe,N Ando et al, 'Transplacental gene delivery (TPGD) as a noninvasive tool for fetal gene manipulation in mice.' (2019) 20/23 *International journal of molecular sciences*. CD Porada, PJ Park & G Almeida-Porada, 'Gestational age of recipient determines pattern and level of transgene expression following in utero retroviral gene transfer' (2005) 11/2 *Molecular therapy* 284.
[148] Thaldar, Shozi and Kamwendo op cit note 145 at 415.
[149] Leslie P Scheunemann & Douglas B White, 'The Ethics and Reality of Rationing in Medicine' (2011) 140(6) *Chest* 1625.
[150] Ellie Tragakes & Mikko Vienonen, 'Key Issues in Rationing and Priority Setting for Health Care Services' 2 <https://www.euro.who.int/__data/assets/pdf_file/0007/118582/E60144.pdf> accessed 26 November 2020.
[151] RD Truog and others, 'Rationing in the Intensive Care Unit' (2006) 34(4) *Critical Care Medicine* 958.
[152] ibid 759.
[153] Scheunemann & White op cit note 149 at 1626–1627.

rationing is a common practice, very few members of the society are aware of the rules that govern it and hence rationing and priority setting usually fall prey to close public scrutiny. This is has become more pronounced given the limited resources as a result of the TB and HIV epidemics.[154]

Accordingly, in deciding how CRISPR therapies for the treatment of TB will be distributed, rationing can either be explicit or implicit. Explicit rationing entails a situation under which the government or local authority implements a transparent criterion which prescribes the circumstances under which certain people will be eligible to access CRISPR therapies over others, whereas under implicit rationing — also known as bedside rationing — the discretion is left with the clinicians to evaluate the competing needs of patients in deciding who to allocate the CRISPR therapies to.[155] Implicit rationing can take the form of any of the following:

> '• rationing by denial, in which care providers turn away would-be patients on the grounds that their needs are not urgent enough;
>
> • rationing by selection, in which service providers accept only the patients with the greatest likelihood of benefiting from the intervention;
>
> • rationing by deflection, in which would-be patients are directed to other programmes or services;
>
> • rationing by deterrence, which, instead of flat denial, makes access to a service more difficult, (by, for example, lack of information on the service, incomprehensible forms, etc.) thus discouraging its use;
>
> • rationing by delay, which discourages demand through the imposition of long waiting periods.'[156]

According to a review of international research and surveys conducted in South Africa, the demand for public healthcare is indirectly rationed via a number of different strategies which include waiting lists and lines up, guarding and controlling access to higher levels of specialist care as well as medication and surgery formularies.[157] This suggests that South Africa has makes use of the implicit rationing model. Hall argues that most governments prefer implicit rationing because it allows the society to believe that one's death is attributable to an

[154] Bettina Taylor, 'NICE Rationing of Specialised Health Care Services for South Africa?' (2008) 98(5) *South African Medical Journal* 368.
[155] Friedrich Breyer, 'Implicit Versus Explicit Rationing of Health Services' 11 <https://www.ifo.de/DocDL/dicereport113-forum2.pdf> accessed 27 November 2020.
[156] Tragakes and Vienonen op cit note 96 at 7.
[157] Econex, 'Modelling the Rationing of Healthcare' <https://econex.co.za/wp-content/uploads/2015/04/econex_health-reform-note_12.pdf> accessed 25 October 2022.

unpleasant fate, and not the outcome of government's rationing decisions or rules.[158] Authors have also argued that implicit rationing encourages doctors to consider the specifics of each patient's medical profile in making their treatment decision as compared to rationing according to strict rules.[159] If this reasoning is anything to go by, access to gene editing services will therefore most likely be decided on a case by case basis, subject to the clinician's medical evaluation. However, it is equally possible that due to the lack of set rationing guidelines and depending on the medical facility one approaches, CRISPR therapies for the treatment of TB may simply be offered on a 'first come first serve' basis.

The case of *Soobramoney v. Minister of Health, KwaZulu-Natal,* as discussed earlier in the chapter, provides insight into the South African legal perspective on the distribution of scarce resources. The Constitutional Court (CC) in *Soobramoney* illustrated that healthcare is a limited resource and that it is necessary to make tough decisions in ensuring that medicals resources are used effectively.[160] Sachs J observed that:

> 'In all the open and democratic societies based upon dignity, freedom and equality with which I am familiar, the rationing of access to life-prolonging resources is regarded as integral to, rather than incompatible with human rights approach to healthcare.'[161]

a) Proportionality and the general limitation clause of the Constitution

The need for CRISPR therapies for the treatment of TB is national, although distributed differently across the populations. As such, who should get access to gene editing services first and who will actually have their genes edited first?

In making such tough decisions, healthcare rationing measures need to be appropriate to the legitimate aim it seeks to achieve. Thus, the gravity of 'the discriminatory measures' must be weighed against the value of the legitimate aim.[162] This raises the question of whether, for instance, rationing CRISPR TB therapies on the basis of age may be considered as a 'proportionate means of achieving a legitimate aim'.

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[158] MA Hall, 'The Problems with Rules-Based Rationing' (1994) 19 *Journal of Medicine and Philosophy* 315–316.
[159] DJ Hunter, 'Rationing of Health Care: The Political Perspective' (1995) 51(4) *British Medical Bulletin* 876–878.
[160] *Soobramoney v Minister of Health* at para 31.
[161] *ibid*.
[162] Julian Savulescu, James Cameron & Dominic Wilkinson, 'Equality or Utility? Ethics and Law of Rationing Ventilators' (2020) 125(1) *British Journal of Anaesthesia* 11.

Section 36 of the Constitution contains the limitation clause. It provides as follows

> 'The rights in the Bill of Rights may be limited only in terms of law of general application to the extent that the limitation is reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom, taking into account all relevant factors, including— (a) the nature of the right; (b) the importance of the purpose of the limitation; (c) the nature and extent of the limitation; (d) the relation between the limitation and its purpose; and (e) less restrictive means to achieve the purpose.'

In asserting the significance of Section 36 in connection to socio-economic rights, Liebenberg contends that;

> 'the State's purpose in limiting a right should not be solely for reasons of administrative convenience, cost-saving or a re-prioritisation of resources. Allowing these reasons to constitute sufficient grounds of limitation will strip the rights of all effect. In order to justify a limitation on these rights under section 36, the State will have to argue that the restriction based on resource constraints is reasonably required in the interests of the general welfare in a democratic society based on human dignity, equality and freedom. In addition, the nature and degree of the restriction must be carefully tailored to fit these purposes (the proportionality test).'[163]

The first stage of the analysis basically entails the interpretation and development of the meaning, nature, content, extent of the right in question and the assessment of whether the offending legislation impairs or limits the defined content of the rights. This entails analysing the right's text in the context of other constitutional provisions, particularly other rights enshrined in the Bill of Rights, historical background of both the constitution and the right, the justifications for its inclusion as a constitutional right and the concepts enshrined in the right.[164] However, despite that the cases of *Grootboom* and the *Treatment Action Campaign* dealt with socio-economic rights, the general limitations clause was not applied. This is because in order for a limitation of rights to be legitimate, it must be contained in the law of general application, which was not the case with the two decisions. However, the case of *Khosa v Minister of Social Development*[165] which involved the Social Assistance Act 59 of

[163] S Liebenberg, 'Violations of Socio-Economic Rights: The Role of the South African Human Rights Commission', *The post-apartheid constitutions: Perspectives on South Africa's basic law* (Witwatersrand University Press 2001) 424.
[164] NW Orago, 'Limitation of Socio-Economic Rights in the 2010 Kenyan Constitution: A Proposal for the Adoption of a Proportionality Approach in the Judicial Adjudication of Socio-Economic Rights Disputes' (2013) 16(5) *Potchefstroom Electronic Law Journal* 198.
[165] *Khosa v Minister of Social Development; Mahlaule v Minister of Social Development* 2004 (6) SA 505 (CC).

1992 was also decided using the criterion of reasonableness and not by conducting a limitation analysis. The Constitutional Court (CC) clearly noted that the difficulty of applying section 36 in socio-economic rights cases was due to the internal restriction requiring the State to go no further than to take 'reasonable legislative and other measures within its available resources to achieve the progressive realisation' of the rights.'[166] Justice Ngcobo questioned whether the criteria for determining reasonableness under Section 27(2) were comparable to those for determining justification and reasonableness under Section 36 but did not offer any guidance on how the two sections might be applied in the context of socio-economic rights. Writing for the majority, Mokgoro J was of the opinion that using either the proportionality analysis or the reasonableness evaluation would produce the same outcomes, and she supported her conclusion by stating that following;

> 'If a legislative measure taken by the State to meet this obligation fails to pass the requirement of reasonableness for the purposes of sections 26 and 27, section 36 can only have relevance if what is 'reasonable' for the purposes of that section, is different to what is 'reasonable' for the purposes of sections 26 and 27.'[167]

The Constitutional Court (CC)'s reasoning has been criticised by scholars such as Iles, who argues that the test for reasonableness as applied in *Grootboom* is not analogous to the test for reasonableness completed under Section 36. He argues that the *Grootboom* reasonableness test is intended to examine the proposal for the realization of the socio-economic right, the manner it will be achieved, the resources to be used and the timing of doing so. However, section 36 demands a somewhat different analysis of reasonableness — whether the limitation of the right is rationally achieving its purpose.[168] He states the following;

> 'Section 36 reasonableness is directed not at a plan for realising rights (as Grootboom reasonableness is) but at an examination of the reasonableness of measures that limit rights. Rights are not limited by plans that are designed to give effect to them. [SERs] are limited rather by a lack of available resources, an alternative policy emphasis by the State, or an omission of certain groups from a realisation plan. Grootboom reasonableness does not involve choosing one value from a cluster of incommensurable values as s 36 reasonableness sometimes does.'[169]

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[166] The Constitution of the Republic of South Africa s 27(2).
[167] *Khosa v Minister of Social Development; Mahlaule v Minister of Social Development* at para 82.
[168] K Iles, 'Limiting Socio-Economic Rights: Beyond the Internal Limitation Clauses' (2004) 20(3) *South African Journal on Human Rights* 456–457.
[169] ibid.

Currie and De Waal argue that since most litigations involving socio-economic rights are concerned with omissions of positive obligations, the analysis under section 36 will be irrelevant due to the requirement of a law of general application.[170] Pieterse, however, argues that if such restrictions are to pass constitutional muster, such limitations must in addition to using the principle of reasonableness, be justified in light of an open and democratic society founded on human dignity, equality, and freedom. He also contends that a proportionality test that takes into account all pertinent factors should be conducted.[171] However, in the case of *Jaftha v Schoeman*[172] which involved the validity of the Magistrates' Court Act which permitted the sale of a person's home in execution of a civil debt, the Constitutional Court appeared to have adopted Pieterse's approach. The Court found that where the State limits those obligations, such a limitation must be justified under section 36. The Constitutional Court recognised the existence of negative socio-economic rights obligations in sections 26(1) and 27(1) of the South African Constitution. As such, the Constitutional Court conducted a limitations analysis in accordance with Section 36 and determined that the violation of Section 26(1) was not reasonable or justifiable in light of Section 36 due to the significance of housing access and its connection to dignity, the gravity of the violation, and the availability of less onerous alternatives.[173]

Without being repetitive, the inclusion of socio-economic rights in the Bill of rights was to remedy the injustices of the past. The right of access to healthcare aims to ensure everyone has access to preventative and curative healthcare services. One could therefore argue that the unavailability or the rationing of CRISPR therapies for the treatment of TB is a violation of the right of access to healthcare services as it infringes on their access to effective medical treatments. On the test set out above, it may be noted that the rationing of healthcare services places a limitation on the right of access to healthcare services. It is therefore necessary to ascertain the justifiability of this particular measure. Section 36 enjoins one to consider the nature of the right and the nature and extent of the limitation in assessing the importance of the purpose of the limitation. It is therefore necessary to highlight the reality that rationing decisions pervade daily practices in our healthcare system.

[170] Iain Currie and Johan de Waal, *Bill of Rights Handbook* (6th edn, Juta Limited 2013) 594.
[171] Marius Pieterse, 'Towards a Useful Role for Section 36 of the Constitution in Social Rights Cases? Residents of Bon Vista Mansions v Southern Metropolitan Local Council' (2003) 120 *South African Law Journal* 45–47.
[172] *Jaftha v Schoeman* (2005 2 SA 140 (CC)).
[173] ibid 35–49.

Conversely, the importance of access to healthcare services particularly for chronic TB patients and its link to the inherent dignity of a person is another possibility to consider. The right of access to healthcare services acts as a furtherance of human dignity since good health transcends mostly from healthcare. The restriction on who may access gene editing services therefore places people who have previously suffered injustices of the past on the basis of race, social status, and other factors in a position of reliving the injustices of the past. It is therefore clear that the unavailability or the limited doses of CRISPR therapies is a severe limitation of the right of access to healthcare services. The purpose of the limitation is important in that it is difficult to comprehend how the limited CRISPR therapies that the South African government will have access to can be made available to everyone at once. It is not easy to adopt a CRISPR roll out approach under which each citizen will benefit equally and timeously. The budgetary circumstances of our country must not be overlooked before a rationing mechanism can be rendered unconstitutional. It is therefore desirable to adopt a roll out mechanism which is based on equity and other factors important in our democratic South Africa. I suggest that although, healthcare rationing is a violation of section 27(1) of the Constitution, it is justifiable.

The second stage of the analysis involves the proportionality test which analyses the reasonableness and justification of the restriction using the section 36 factors in the context of a democratic society founded on human dignity, equality, and freedom. The principle of proportionality has been the most important balancing tool in constitutional rights when a right must be weighed against a competing right or interest. Although, there are different formulations of the principle, the principle is about resolving of a conflict between the right and a competing right or interest, and this conflict is ultimately resolved at the balancing step.[174] It is therefore crucial to show that there is a genuine conflict between the right and a pertinent competing interest (legitimate objective) that cannot be resolved in a less restrictive manner.

Nevertheless, there seems to be consensus on the elements of proportionality analysis,[175] and as such, a proportionality analysis is required to have the following four step inquiry. First, the policy that infringes on the right must have a justifiable purpose (legitimate goal stage). The second inquiry is that there must be a rational connection between the policy and the

[174] Dieter Grimm, 'Proportionality in Canadian and German Constitutional Jurisprudence' (2007) 37 *University of Toronto Law Journal* 383.
[175] IM Rautenbach, 'Proportionality and the Limitation Clauses of the South African Bill of Rights' (2014) 17(6) *Potchefstroom Electronic Law Journa*l 2233.

accomplishment of the aim (rational connection or suitability stage). Third, there must be no less intrusive alternative that is similarly effective (necessity stage). Lastly, the law must not place an excessive burden on the right-holder (balancing stage).[176]

The legitimate stage assesses the said policy's 'goal', that is, which goals are, and which are not legitimate in the strict sense. The Constitutional Court typically avoids probing the motivations behind the decision-makers but rather whether a policy or choice is objectively justifiable. Therefore, the first question to answer when assessing the legitimacy of a policy that interferes with a right is whether there are any interests that are candidates for justifying the interference in the sense that it is not entirely implausible that they will at least be rationally connected to the policy.

Take the case of rationing CRISPR TB therapies on the basis of age on the ground that making CRISPR therapies (particularly, germline editing) available to individuals of child-bearing age could accelerate the pace at which we achieve herd immunity against TB. Authors such as Savulescu have suggested what is known as a 'precautionary utilitarian' approach.[177] This approach serves to minimise arbitrary discrimination while at the same time acknowledging that certain decisions have to be made for the greatest population. An interest that would be a candidate for justifying the rationing is the need to achieve herd immunity faster with the limited CRISPR therapies available; therefore, the protection of public health would serve as a goal (which would obviously be legitimate).

Once, the legitimate aim has been established, the purpose of the appropriateness stage is to determine the degree to which the interference achieves the legitimate goal. That is, the interference must be a suitable means to at least partially achieve the goal. If the interference aids in the achievement of the goal even in a minimal way, the appropriateness test is satisfied because it has been proven that there is a conflict between the two values.[178] In the hypothetical scenario given, it is clear that limiting access to the CRISPR therapies infringes on other persons right of access to healthcare services. The third stage (necessity stage) then calls in assessing whether there is no less stringent policy that accomplishes the legal objective just as effectively. As already stated, the South African Constitution guarantees everyone the right of access to healthcare services.[179] In the present case, difficult decisions ought to be made to

[176] ibid 2233–2234.
[177] Savulescu, Cameron and Wilkinson op cit note 158 at 13.
[178] Kai Möller, 'Proportionality: Challenging the Critics' (2012) 10(3) *International Journal of Constitutional law* 709, 713.
[179] The Constitution of the Republic of South Africa s 27.

maximise the benefit that may be obtained from the limited CRISPR therapies. This entails that a certain population group would have to be put at a disadvantage in accessing CRISPR therapies if it ascertained that such population group would significantly benefit less from gene editing as compared to the other. Minimal differences in chances of improved quality of life ought to be ignored so as not to amount to unreasonable discrimination. More so, if germline editing is reserved to those of childbearing age (for the legitimate reason already stated), then, it may not be necessary to also restrict access to gene therapy services (somatic editing) to the same population group that has been restricted access to germline therapy, because the goal of herd immunity may already have been achieved by the initial restriction itself.

The goal of the final stage — balancing stage — is to choose which of the two (or more) values that are at risk is more important under the specific conditions of the case. In other words, the issue is whether the protection for the competing right or interest justifies the interference with the right. The two values must be 'balanced' against one another in order to achieve this. Möller avers that there are two ways to balance. The first classification is referred to as 'interest balancing' wherein it functions in accordance with a cost-benefit analysis, in which the weights of the various rights or interests are weighed and then compared. The second classification is referred to as 'balancing as reasoning.' This involves making a moral case for which of the conflicting interests in the situation should take precedence, and that moral case may or may not involve interest balancing.[180] He further states that it must be borne in mind that balancing in constitutional rights law does not necessarily refer to interest balancing.[181]

In applying the interest balancing exercise, it is important to highlight that underlying problem raised by the rationing mechanisms is not mere unwillingness to make CRISPR therapies available but, limited resources. Rationing happens because of general fiscal scarcity rather than an absolute scarcity of the particular medical resource. The CRISPR therapies will eventually be rolled out to everyone, but it has to happen in phases. Furthermore, in as much as the State has a duty to recognise the sanctity of human dignity and take steps to maintain and enhance it, the good of the community (achieving herd immunity) should also be taken into consideration. This is where individual interests versus community interests come into play. Ferguson and Chaplan argue that we, as moral agents, regularly form relationships with one another within our society which then provides us with moral reasons to act in a certain

[180] Möller op cit note 178 at 715.
[181] ibid.

way towards specific people as compared to others.[182] In the context of CRISPR therapies, this implies that some members of the society will have the, not the right, but the privilege of having easier access to CRISPR therapies. As per Singer:

> No doubt we do instinctively prefer to help those who are close to us. Few could stand by and watch a child drown; many can ignore the avoidable deaths ... The question, however, is not what we usually do, but what we ought to do …[183]

b) Who should have access to gene editing first?

The CESCR has set minimum core obligations and whether they are referred to as benchmarks or essential commitments, what is important is the understanding that action must always be staggered because the reality of limited resources makes it nearly impossible to offer CRISPR therapies to every person at once. No State can ever claim to have achieved full realisation of the right to health since the formulation of the CESCR. Therefore, it would then be disingenuous to scoff at the reality of needing incremental progress over time. This phased action will need to include a starting point, have a start date, and accountability indicators. Given the anticipated constrained supply of CRISPR therapies versus its high demand for due to high disease burden, there is need for clear guidelines on the equitable distribution of CRISPR therapies — who will receive CRISPR, and who will not. Accordingly, a number of regulatory or oversight measures will need to be put in place before gene-editing technology is rolled out to the masses especially if we want to prioritise highly vulnerable populations. Thus, without proper regulatory measures, the healthcare system will experience difficulties in transitioning seamlessly to the next phase of the epidemic response — treatment and immunisation using CRISPR. As a consequence, pre-existing health and socioeconomic inequalities would be exacerbated.[184] Therefore, in making CRISPR therapies available to the general population, the government's roll out program must satisfy the reasonableness approach as laid out in the case of *Grootboom*. It must be comprehensive, coherent and coordinated. The CRISPR roll out program must be balanced and flexible, reasonable and make appropriate provision for short, medium and long-term needs. Most importantly it must not

[182] Kyle Ferguson & Arthur Caplan, 'Love Thy Neighbour? Allocating Vaccines in a World of Competing Obligations' (2020) *Journal of Medical Ethics* 3.
[183] P Singer, *Practical Ethics* (3rd edn, Cambridge University Press 2011) 202–203.
[184] Yangzi Liu, Sanjana Salwi & Brian Drolet, 'Multivalue Ethical Framework for Fair Global Allocation of a COVID-19 Vaccine' (2020) 46 *Journal of Medical Ethics* 500.

exclude a significant sector of society and must take account of those who cannot pay for services. In the next section I propose five guiding principles as formulated by the Strategic Advisory Group of Experts on Immunisation (SAGE).[185] Although, the Framework was formulated with the aim of ensuring equitable distribution of COVID19 vaccine, I am of the view that the principles articulated in the framework could equally assist with equitable allocation of CRISPR therapies for optimal impact.

Principle	**Objectives**
Human Well-Being	Its purpose is to protect and promote health by reducing deaths and TB disease burden by devising strategies that reduce societal transmission;
Equal Respect	Regards all human beings —regardless of race, age, economic standing etc — as having equal moral standing and as worthy of equal moral consideration in the allocation of CRISPR therapies. This will ensure that all individuals who qualify under the priority setting criteria have a meaningful opportunity to access gene editing services in healthcare facilities.
Equity	This is to ensure that initial limited CRISPR therapies mostly benefit groups experiencing the greatest disease burden. As such, rationing of CRISPR therapies should consider the vulnerabilities and risks of different population groups. The government is therefore bound to take proactive measures to ensure equal access to gene editing services for everyone who qualifies under a priority group. Particularly, this calls upon the government to ensure that all South Africans have access to gene editing services regardless of their financial capabilities or geographic location.
Reciprocity	Offering gene editing services to those, who due to their occupation, take or bear exceptional risks of TB infections. In this instance, the purpose of gene editing services will be to provide immunity against TB.

[185] World Health Organization, 'WHO SAGE Values Framework for the Allocation and Prioritization of COVID-19 Vaccination' <file:///C:/Users/tamzy/Downloads/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf> accessed 21 December 2020.

Legitimacy	This necessitates the government to make decisions regarding the allocation of CRISPR therapies through open processes based on shared values, accurate scientific evidence, and adequate representation and input by society members (transparent consultation).

The framework illustrated by Table 2 shows that promoting access to gene-editing technology compels us to take economic, ethical, and epidemiological considerations in deciding how CRISPR therapies are to be distributed.[186] While these guiding principles may assist in identifying the target groups, these principles are not ranked in any order and as such, target groups that require to be given top priority cannot be easily identified. At times, a decision will have to be made on which principle to prioritise when several come into conflict, or which target groups to prioritise due to restrained supply of CRISPR therapies when all may otherwise qualify for gene editing services.

Nonetheless, in the next section, I identify target groups that correspond to the objectives of the guiding principles. There may be compelling moral reasons to suggest that CRISPR therapies should first be inoculated to the most vulnerable populations.[187] However, with a country like South Africa that is highly burdened by TB infections and tainted with existing healthcare inequalities, prioritising who should get access first may seem a difficult task. In deciding who should get access to gene-editing technology, there is need to ensure that this is executed in a manner that consensual and creates confidence in the healthcare system. Accordingly, Table 3 below identifies a number of unranked priority groups for access to gene editing services.

Table 3: Translating the guiding principles to unranked priority groups for gene editing.

Principle	**Objectives**	**Target groups to consider**
Human Well-being	Reducing TB related deaths and disease burden through treatment and	• Current TB patients especially MDR-TB patients • Populations with significantly elevated risk of being infected (example: persons living in

[186] Harald Schmidt, 'Vaccine Rationing and the Urgency of Social Justice in the Covid-19 Response' [2020] *Hastings Centre Report* 48.
[187] ibid 49.

	immunisation in an equitable manner	denser communities which are also characterised with high TB infection rates • Persons with comorbidities determined to be at significantly higher risk of contracting TB e.g., persons living with HIV •Sociodemographic groups— age groups— at disproportionately higher risk of severe disease or death such as children under 5 years
Reciprocity	Protecting the continued functioning of essential services, including health services	•Healthcare workers especially those involved in the care of TB patients

The primary purpose of healthcare systems is to maximise health through disease prevention and treatment. As such, the considerations identified in Table 3 illustrate that in maximising the benefits of limited CRISPR therapies, multi-drug resistant TB patients, persons with comorbid illnesses such as HIV, children and those TB patients whose epidemiological modelling which suggests that they are likely to spread TB due to their living/social profile should be given priority to access gene editing services for the treatment of TB.

Studies have indicated that most people infected with TB live in overcrowded informal settlements.[188] A tragic reality is that these informal settlements have generally been identified as areas of high deprivation in accessing healthcare services. Therefore, in the quest to curb the TB epidemic, this necessitates prioritising people from these communities because the denser living conditions and lack of access to healthcare services increase transmissibility thus further contributing to more disease burden.[189] It is also important to note that these target groups identified may need to be further refined to ensure that access to gene-editing technology is equitable based on race, gender, location and other factors which often contribute to inequities within the South African healthcare system.

[188] Tahira Kootbodien and Kerry Wilson, 'Tuberculosis Mortality by Occupation in South Africa, 2011–2015' (2018) 15 *International Journal of Environmental Research and Public Health* 4.
[189] Liu, Salwi & Drolet op cit note 184 at 500.

VI. CONCLUSION

The promise of human genome editing to remedy the TB disease burden is profound. As such, the arguments presented in this chapter have highlighted how the right of access to healthcare services is germane to the sustainable accessibility and enjoyment of CRISPR therapies. This rights approach to the issue of accessing gene-editing technology is important because it provides a solid ground to demand access to this technology as well as guiding the standard for rationing these therapies to achieve the goal of fulfilling, protecting, respecting the right of access to healthcare services. While there may be uncertainties in terms of people who may actually have access to these therapies first, it is reasonable if safeguards can be put in place to ensure that this technology is made as widely accessible as possible—at least in the South African setting. As Thaldar et al suggest, the starting point should be emancipating germline editing from the IVF lab by exploring other CRISPR delivery methods. Accordingly, the foregoing discussion has highlighted how policymakers, to ensure equity, ought to ensure that this novel treatment is also accessible to vulnerable yet underserved populations. Ultimately the success of gene editing in emolliating the TB epidemic across all population groups will depend on government's rationing strategies.

CHAPTER 5

THE THEORY OF INTERGENERATIONAL JUSTICE: SERVING HEALTH JUSTICE FOR ALL GENERATIONS?

'Our perfect biological future can now be designed—but who gets to choose?'
— J.S. Morrison

I. THE THEORY OF INTERGENERATIONAL JUSTICE

The TB epidemic threatens the ability of future generations to fully enjoy their human rights. 'Historically pandemics have forced humans to break with the past and imagine their world anew. This one is no different. It is a portal, a gateway between one world and the next.'[1] The TB epidemic therefore raises concerns about intergenerational solidarity and justice prominently in the potential use of gene-editing technology to emolliate TB. But, as much as technological advancements bring immeasurable advantages to the society, they also pose risks and socio-economic effects to both current and future generations. When deciding to use gene editing technology to avert TB, the effects of such technology are often not fully understood. That is, due to the inherent risk of error associated with human genome editing, these errors may be transmitted from one generation to the next. Consequently, the irreversibility of such decision becomes a significant factor to act responsibly towards future generations.[2]

At the same time, amidst the risks, the potential advantages of heritable genome editing will also be passed along — TB susceptible genes will not be passed down to future generations. Exposure to a risk of harm is not wrong, as Smith et al claim, if the potential benefits and risks of such decisions are taken into consideration.[3] In addition to having a duty to act in their

[1] A Roy, 'The Pandemic Is a Portal' *Financial Times* (3 April 2020) <https://www.ft.com/content/10d8f5e8-74eb-11ea-95fe-fcd274e920ca> accessed 22 August 2022.
[2] Jennifer Kuzma & Lindsey Rawls, 'Engineering the Wild: Gene Drives and Intergenerational Equity' (2016) 56 *Jurimetrics* 283.
[3] KR Smith, S Chan & J Harris, 'Human Germline Genetic Modification: Scientific and Bioethical Perspectives' (2012) 43 *Archives of Medical Research* 504.

children's best interests, parents also have a responsibility to make choices that could be advantageous to them.[4] de Miguel Beriain avers that;

> 'it seems absurd from a moral point of view to consider that a general avoidance of human germ line editing would free us from all types of responsibility to our descendants. Would anyone hold that we would take no moral responsibility for allowing someone to be born with Huntington's disease if we had a tool to cure him or her? It seems clear that the answer to this question must be a resounding "no."[5]

This chapter therefore discusses how the rights of the present generation ought to be properly balanced with those of the future generation. In this discussion, the theory of intergenerational justice will not serve as a limitation but rather as a reminder of what we (the current generation) owe the future generation — to emolliate the TB epidemic through human genome editing.

The concept of intergenerational justice was introduced by John Rawls.[6] He asserts that where there is an intergenerational conflict of interest, factors of justice may oblige current generations not to adopt policies which impose an unfair allocation of expenses and advantages between generations.[7] In essence, the intergenerational justice argument demands that expending actions that threaten future generation's interests are unjust and should not be adopted. Jana Thompson suggests 'a society is intergenerationally just when each generation does its fair share to enable members of succeeding generations, both inside and outside its borders, to satisfy their needs, to avoid serious harm and to have the opportunity to enjoy things of value.'[8] Thompson's narrative of intergenerational justice is extensive in that it extends responsibilities beyond family and even national boundaries. It implies an infinite number of generations and a wide range of safeguards to be put in place. This also suggests that the wants of the living cannot take precedence over the needs of future generations. In a way, Thompson's definition also guards against substantial harm. To prioritize the interests of the living over the needs of or injuries to future generations would be 'profligate', in Gardiner's words. Gardiner

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[4] ibid.
[5] Iñigo de Miguel Beriain, 'Should Human Germ Line Editing Beallowed? Some Suggestions on the Basis of the Existing Regulatory Framework' (2019) 33 *Bioethics* 108.
[6] In 1971 his *magnum opus* 'A Theory of Justice' was released and included a chapter on intergenerational justice. The question of intergenerational justice was arrived at in determining the minimum number of resources that an individual requires in a specific community to lead a minimally decent life. He acknowledges that this amount is greatly affected by what savings earlier generations have done. See J Rawls, *A Theory of Justice* (The Belknap Press of Harvard University Press 1971) 284.
[7] L Meyer, 'Intergenerational Justice' [2019] *The Stanford Encyclopedia of Philosophy* (Summer 2016 Edition) <https://plato.stanford.edu/archives/sum2016/entries/justice-intergenerational/>> accessed 16 June 2019.
[8] J Thompson, 'Identity and Obligation in a Transgenerational Polity', *Intergenerational Justice* (Oxford University Press 2009) 5.

avers that we the living are the 'profligate generation', consuming the future for trivial pleasures. As such, existing generations cannot deny future generations their needs.[9] Edward Page conceives of intergenerational justice as '…concerned with the equitable distribution of benefits and burdens across different generations.'[10] Page appears to provide a more concise definition which appears to be less demanding than Thompson's. Page, unlike Thompson, does not oblige us to consider spatial distance in addition to temporal distance. However, on both accounts it is clear that living persons have duties and obligations to future generations to; bequeath an environment which can satisfy their needs, do them no harm, and allow for some minima of wellbeing.

These are strong specifications in terms of intergenerational relations. What exactly is a fair share? How can it be measured? There are a lot of disagreements over what constitutes a fair share of social burden. In terms of human genome editing, How can we define 'fair share' when one side, the party bearing the biggest burdens (future generation), lacks a voice? Winter further argues that 'things of value' are already contested among the living. How then can we ascertain what the future generation will value? Winter suggests that we can argue that since future generations are unrepresented; we must assume they will value what we value.[11] Contractarians contend that while current generations have the ability to bestow benefits and burdens on future generations, future generations cannot reciprocate to current generations.[12] Benefits may be shared, but not obligations. Giving up a potential advantage in the present for the future pleasure of an unknown future generation, a generation who may not exist if we act in this manner, appears unjust.[13]

Hence, the theory requires that each generation possess a certain level of knowledge to identify the key risks to future well-being posed by any given act. The application of this theory requires a great deal of caution as its arbitrary application can greatly stifle innovation in the healthcare sphere due to the fear of creating injustice to the future generation. This encompasses a situation where future generations have valid claims or rights against the current

[9] SM Gardiner, 'A Perfect Moral Storm: The Ethical Tragedy of Climate Change', *Environmental Ethics & Science Policy Series* (Oxford University Press 2011b) 153.
[10] EA Page, 'Intergenerational Justice of What: Welfare, Resources or Capabilities?' (2007b) 16(3) *Environmental Politics* 453.
[11] Christine J Winter, 'The Paralysis of Intergenerational Justice: Decolonising Entangled Futures' (PhD thesis, The University of Sydney 2017) 41.
[12] BH Weston, 'The Theoretical Foundations of Intergenerational Ecological Justice: An Overview' (2012) 34(1) *Human Rights Quarterly* 251–266.
[13]Parfit D, *Reasons and Persons* (Oxford: Oxford University Press, 1984).

generation, which in turn is subject to corresponding responsibilities towards future generations. In the past, intergenerational issues were primarily focused on the ecosystem. However, the concept has now evolved to include a wide range of concerns including the health of future persons. The theory of intergenerational justice therefore sits at the heart of concern for future generations.

> 'Throughout the ages, mankind has, for economic and other reasons, constantly interfered with nature … Owing to new scientific insight and to a growing awareness of the risks for mankind—for present and future generations—of pursuit of such interventions at an unconsidered and unabated pace, new norms and standards have been developed, …. Such new norms have to be taken into consideration, and such new standards given proper weight, not only when States contemplate new activities but also when continuing activities begun in the past…'[14]

The above quote demonstrates the concept that innovation must meet the needs of the current generation without jeopardising future generations' ability to meet their own. Accordingly, the theory of intergenerational justice is concerned with the respect for the rights and duties of the past, present and future generations.[15]

However, while human rights law is experienced in dealing with the rights of existing persons, its application to future generations presents several issues. Is it reasonable to say that future persons have human rights and that the current generations owe them equivalent obligations? Secondly, if such obligations exist, how should they be balanced against possibly conflicting rights of the current? Most importantly, assuming harm to future persons is done, what are the mechanisms used to enforce responsibilities owed to future persons who by their inexistence are unable to institute claims to enforce their rights?

The theory of intergenerational justice is therefore challenging to frame as it forces us to consider the rights and responsibilities across generations as a generational contract. It is based on the concept that all generations should partner to ensure the survival and well-being of humans.[16] It also raises vexing questions about the meaning of terms that we may have taken for granted, such as generation. How a generation is described influences the length of a generation. For instance, defining a generation to mean that no one living today can interact

[14] *ICJ Case Concerning the Gabcikovo-Nagymaros Project (Hungary v Slovakia)* (Judgement of 25 September 1997, 37 ILM, 1998) 162 para 140.
[15] Tayler J, 'Intergenerational Justice: A Useful Perspective for Heritage Conservation' [2013] *CeROArt* 1.
[16] Kuzma and Rawls op cit note 2 at 282.

with any of the next generation implies that generations can last up to 200 years. If this definition of excluding mutual interaction is anything to go by, this translates that justice is owed to persons to be born 200 years from now. More so, the obligation of justice also extends to non-overlapping generations. This is problematic because the huge gap from one generation to the next raises uncertainty about the consequences of our actions or the nature of the choices of future generations.[17] In light of germline gene editing, this principle then raises an important question; should one generation have the power to edit the genes of the next generation without their consent? Secondly, do these justice obligations only apply to contemporaries or do they extend to future people?[18]

There have been different responses to the question 'between whom does intergenerational justice apply?' The table below illustrates the kind of 'subjects' involved in the context of justice between generations.

	Subjects of intergenerational justice	**WHO owes…**	**…WHOM**
Lukas Meyer[19]	Non-contemporaneous generations	- Present generations…	…future generations …past generations
Nancy Jecker[20]	Age groups	- Society… - Specific age groups (eg: middle-aged adults)…	…specific age groups (eg: the elderly)
Joerg Tremmel[21]	Generations	- Present people… - Older generations…	…future generations …young generations (i.e. young people and children)
Axel Gosseries and Lukas Meyer[22]	Non-contemporaneous generations; overlapping generations; age groups; birth cohorts.	- Present people… - Society… - Birth cohort X…	…future generations …past generations …specific age groups …birth cohort Y

Table 4: Between whom does intergenerational justice apply?

[17] Axel Gosseries, 'On Future Generations' Future Rights' (2008) 16(4) *The Journal of Political Philosophy* 447.
[18] RB Howarth, 'Intergenerational Justice and the Chain of Obligation' (1992) 2(1) *Environmental Values* 133.
[19] Meyer op cit note 7.
[20] Nancy Jecker, 'Intergenerational Justice', *Encyclopedia of Aging* (Macmillan Reference USA).
[21] Jörg Tremmel, 'A Theory of Intergenerational Justice' (PhD, Heinrich-Heine-University Dusseldorf 2008).
[22] Axel Gosseries and Meyer Lukas, *Intergenerational Justice* (Oxford University Press 2009).

The table above demonstrates that despite the fact that 'generations' are the constant focus of intergenerational discussions, we could indeed speak of a variety of intergenerational relations, including those between the present and past generations, the present and the future generations and overlapping generations. Thus, intergenerational justice deals with problems that affect persons who were born at different times. The focus of this chapter is on relations between non-contemporaneous generations. Lukas Meyer contends that the fact that intergenerational justice is focused on individuals who will never coexist in the future distinguishes it as a distinct area of philosophical inquiry.[23] He compares this with other aspects of social justice, which are focused on what modern people, or groups of people, owe to one another. He understands the objects of intergenerational justice as being future and past generations.[24]

With respect to heritable human genome editing, the present generation has one important, arbitrary advantage over future generations, namely, they can enjoy the benefits of gene editing without incurring risks of harm that may only materialize in subsequent generations. Equally, the present generation is in a complicated position. On the one hand, it has an advantage over its successors, namely, that it can choose to benefit from this technology, externalising a range of risks of harm for future generations to bear. On the other hand, it also has the disadvantage of being the first to become aware of these risks of harm and hence could lead to additional obligations on the current generation that are burdensome.

Alexal Gosseries poses the question of whether future generations should even be given ethical and/or legal rights? This question is crucial to this current debate as it calls for a critical analysis of both the philosophical realm and the realm of realistic proposals arising from a desire to protect future generations.[25] Weiss further questions whether it is possible to speak of intergenerational obligations without their corresponding rights, and whether these obligations can exist without rights. The word 'right' although appearing frequently in legal discourse, is also the one that is most difficult to define. A right, according to Hohfeld, is a legal interest that imposes a correlative duty.[26] Hohfeld did not give much attention as to how rights and duties relate to one another. He avers that the word 'rights' is misused to refer to things that, while occasionally being a privilege, power, or immunity, are not true rights in the strictest sense. Hohfeld provides us an analytical framework that divides rights into four types of jural

[23] Meyer op cit note 7.
[24] ibid.
[25] Gosseries op cit note 17 at 446.
[26] JM Balkin, 'The Hohfeldian Approach to Law and Semiotics' (1990) 44 *University of Miami Law Review* 1119, 1119.

relationships— right versus duty, liberty versus no right, power versus liability and immunity versus disability.[27]

right	**liberty**	**power**	**immunity**
duty	no right	liability	disability

The four sets of distinct Hohfeldian jural relations are represented in the table above. The bottom row shows the legal position that each of Hohfeld's four forms of legal rights entails for the opposing party. Hence, it is important to note that all of the Hohfeldian rights (in the top row) inevitably represent entitlements. A way to restrict the word right to its precise meaning is by applying the correlative (and equivalent) duty as rights are always coupled with legal obligations.[28] Therefore, if X is said to have a legal claim-right, he is therefore legally protected from Y's interference. According to the correlativity stipulation, if X has a claim-right against Y, Y owes X a duty. MacCormick critiques Hohfeld's view of rights by stating that a legal right is not (or does not) have to be correlative to a duty placed upon some other individual. Thus, he states that 'to rest an account of claim rights solely on the notion that they exist whenever a legal duty is imposed by a law intended to benefit assignable individuals ... is to treat rights as being simply the 'reflex' of logically prior duties.'[29] He further notes that a law conferring a right is best understood in terms of a typical purpose to give some kind of benefit. When such a benefit is granted, the law will then offer that person a normative protection, which may involve any or all of the numerous forms defined by Hohfeld such as duties, disabilities, and other restrictions placed on others.[30] Therefore, MacCormick sees legal rights as grounds of duties, or reasons for imposing duties rather than simply being a correlative of the duty.

According to John Austin's classification of duties, intergenerational obligations are absolute duties that occur independently of any correlative right. He described these set of duties as those that prescribe duties towards non-obliged parties who are not determinate persons.[31] However, Weiss counterargues that this line of reasoning is flawed. He states that if the current generation's obligations are mere absolute duties then the current generation may

[27] Nokolai Lazarev, 'Hohfeld's Analysis of Rights: An Essential Approach to a Conceptual and Practical Understanding of the Nature of Rights' [2005] *Murdoch University Electronic Journal of Law*.
[28] ibid.
[29] DN MacCormick, 'Rights in Legislation', *Law Morality and Society* (Oxford University Press 1977) 197.
[30] ibid 197–199.
[31] CK Allen, 'Legal Duties' (1931) 40(3) *Yale Law Journal* 352.

be biased in formulating the obligations to favour their own interests at the expense of future generations.[32]

The theory of intergenerational justice is built on the premise that all generations should partner to ensure the survival and well-being of humanity.[33] Future generations are therefore perceived to have legitimate claims against the current generation whereas the present generation has correlative duties to future generations.[34] The difficulty in establishing intergenerational justice pertaining to germline editing lies in constructing policies that in reality represent the interests of future generations. The reality is that the current generation can be said to only represent the interests of their immediate descendants. They are less likely to be concerned with generations in the far future and hence the interests of the latter can only be said to be rudimentary at the moment.

Spijkers avers that by definition there are no future generations now, therefore they cannot be the current bearers or subjects of anything, including rights.[35] Professor Anthony D'Amato agrees with this sentiment and invokes Derek Parfit's non-identity problem in his argument. He argues that future generations cannot have rights because they do not yet exist and therefore whatever action we take today (whether good or bad) affects them by robbing some potential members of future generations of their existence (different people will be born as a result of the action taken).[36] In response, Weiss contends that the rights discussed in light of intergenerational justice do not belong to individuals but rather are group (generational) rights. These are rights held by one generation in relation to the other. More so, since the rights exist as generational rights which are a new era of human rights, it does not matter if another group of individuals emerges as argued by D'Amato. What is pertinent is the existence of an individual from the future generation regardless of who they are. She concludes by stating that D'Amato's line of reasoning is erroneous in that it gives a very constrained view of 'human rights' that are useful in underpinning sustainable development arguments.[37]

[32] Charles Weiss, 'Scientific Uncertainty and Science-Based Precaution' (2003) 3(2) *International Environmental Agreements: Politics, Law & Economic* 204.
[33] Jennifer Kuzma & Lindsey Rawls, 'Engineering the Wild: Gene Drives and Intergenerational Equity' (2016) 56 *Jurimetrics* 282.
[34] Tayler op cit note 15 at 3–4.
[35] O Spijkers, 'Intergenerational Equity and the Sustainable Development Goals' (2018) 10 *Sustainability* 4.
[36] A D'Amato, 'Do We Owe a Duty to Future Generations to Preserve the Global Environment?' (1990) 84(1) *American Journal of International Law* 196–198.
[37] Weiss op cit note 32 at 203–205.

However, I suggest that although it may be theoretically feasible to imagine future generations as having rights, there are considerable practical and legal obstacles to this human rights-based approach which are discussed in the next section. Applying the human-rights-based approach requires a great deal of caution as its arbitrary application can greatly stifle the clinical translation of CRISPR therapies due to the fear of causing injustice to future generations. Consequently, the theory of intergenerational justice is a possible limitation to human genome editing as one should consider to what extent the present generation should forgo their rights or entitlements to uphold the rights of future generations.

The next section highlights the essence of the challenges in recognising 'rights' of the distant future generations, as well as the potential solutions to these challenges.

a) Unpacking intergenerational rights

i. Intergenerational relationships and responsibilities

As per Rehmann-Sutter:

> 'My body was not "built" by my parents and the genome was not "written" by them. I am glad, otherwise I would perhaps blame them for all the mistakes and limitations within it. It was rather the nature of their bodies that created my body.'[38]

Do you ever have similar thoughts about yourself? This is an intriguing concern whether Rehmann-Sutter's sentiments would still be the same had he learnt that the parents had the power to change his so-called fate through human genome editing? Perhaps so. Rehmann-Sutter suggests that the parent-child relationship should be viewed as generative.[39] Generative parenting may be described as the commitment to care for the future generations through striving to address the needs of one's children.[40] It is about the biological connection between generations thus making the germline is a generative entity.[41] The use of gene editing technologies is likely to either positively or negatively affect the fundamental aspects of intergenerational relationships.[42] Rehmann-Sutter has argued that when deciding to opt for

[38] Anne-Floor J de Kanter, 'Germline Editing: Intervening in Parent-Child Relationships. An Analysis of Rehmann-Sutter's Biology and Phenomenology of the Germline and the Argument of Relationality' (Master of Arts in Applied Ethics, Utrecht University 2019) 1.
[39] ibid at 69.
[40] Sean E Brotherson, David C Dollahite & Alan J Hawkins, 'Generative Fathering and the Dynamics of Connection between Fathers and Their Children' (2005) 3(1) *Fathering* 3.
[41] de Kanter op cit note 38 at 31.
[42] de Kanter op cit note 38.

germline editing, for instance, parents have to be able to explain this choice to their child convincingly. Parental responsibility in germline editing is therefore at least partly expressed in their need to explain and account for this decision.[43] Hence, if the parents do not succeed in constructing a narrative that they consider sufficiently forceful in explaining the decision to their future child, they may choose to abstain from the intervention instead. On the other hand, such narrative construction will help the parents to be explain their choice as an expression of their love for their progenies.

To derive a sense of the difficulty parents may be faced with in deciding to make use of gene-editing technology, consider Marda who just learnt that she has a Sickle Cell trait. Marda knows that even though her partner, Steven, has the normal type of haemoglobin, there is a fifty per cent chance with each pregnancy that their children might be born with the sickle cell trait. Do you think it is wise for Marda to bring children into the world with such a trait when it could be prevented through germline editing? What happens if Marda's offspring conceive children with persons who are also carriers of the trait? Simple - the disease, Sickle Cell Anaemia, will strike Marda's grandchildren.

One might assume that Marda would be relieved to learn that she has been spared of the disease by being a mere carrier. It is also possible that Marda might not care if she or her offspring are carriers of this trait. In fact, she may consider it the nature of their bodies, as Rehmann-Sutter puts it. However, as a prospective mother and grandparent, she may have 'survivor's guilt' and wonder if her descendants will also be spared from this disease. The Talmud, a Jewish holy script, tells a compelling parable:

> 'An old man is asked why he is planting a carob tree, as after all he will not live to see this tree bloom. He answers: "When I was born the world was full of blooming carob trees."[44]

In putting this parable into context, we feel obligated to leave something for future generations because the previous generation did it for us, which is a valid concept of intergenerational reciprocity. Marda might find this as a compelling reason to safeguard the wellbeing and quality of life of her descendants through human genome editing. It is not necessary that Marda's forefathers should have made a similar sacrifice, but intergenerational reciprocity lies in acknowledging that she would not be enjoying the quality of life she has now if it were not for their efforts or sacrifices such as through environmental conservation.

[43] ibid 28.
[44] Tremmel op cit note 21 at 212.

On the other hand, Marda being a mere carrier would ask, why should I bother with germline editing? Why should I be the one doing anything for posterity? What have past generations done for me? Remember, intergenerational justice does not imply that the current generation must sacrifice itself for the next one. As per Jörg Tremmel, intergenerational justice is merely an enabling advancement.[45] Because of the autonomous nature of intergenerational obligations, Marda gets to decide if germline editing is necessary in the circumstances.

What preliminary conclusion can be drawn from the concept of intergenerational justice? If the core element of the theory of generational justice is the need for improving the wellbeing of the next generation, then Rehmann-Sutter's framework on relationality emphasises the significance of understanding the impact of germline interventions could possibly have on intergenerational relationships. More so, if intergenerational justice entails increasing future generations' life chances and living conditions to the greatest extent possible, then the link between intergenerational justice and the TB epidemic is apparent. In the next section, I discuss the possible content of the intergenerational rights as a base of contributing to the mainstream ethical debate on intergenerational responsibilities.

ii. The possible content of the rights

The central argument in debates about intergenerational rights is the argument of relationality. This then calls us to question intergenerational relationships as well as the rights and responsibilities that generations carry. As already stated, it has been questioned whether it is possible to speak of intergenerational obligations without their corresponding rights.[46] It is often argued that if past generations can be said to have rights, then we may also consider the possibility that future generations have rights too. As such, the concept of intergenerational rights could assist us not only with issues of restoration but also with issues of what we owe to future generations. In the same way that the interests of the current generation have the status of rights thus requiring special protection, some future people's interests also require special protection. Therefore, if we are to classify them as rights, we cannot simply outweigh or compromise these rights if they conflict with the interests of the current generation.[47] But is it a valid analogy?

[45] ibid 218.
[46] Weiss op cit note 32 at 203.
[47] Richard Vernon, 'Intergenerational Rights?' (2009) 9(1) *Intergenerational Justice Review* 9.

To begin, we must define what a right is. Rights may be loosely defined as 'entitlements (not) to perform certain actions or entitlements that others (not) perform certain actions'.[48] The use of the word 'rights' thus implies the legitimacy of entitlements. In particular, to imply that someone (future person) has a right is to say that they have an interest in which others (current generation) are obligated to respect. Gaillard describes rights of future generations to be two-fold; environmental rights (sustainable development) and bioethical rights (protection of the human condition).[49] In terms of bioethical rights, this implies the current generation is tasked to take on the fight against TB on behalf of future generations through germline editing.

Let us suppose that another set of rights — intergenerational rights — exist, then there would be something other than the exercise of a moral claim on us by future generations. Put differently, there would be a right-based entitlement. Moreover, Vernon argues that we should not mistakenly think that future generations must be aware of a harm to their interests in order for it to be considered a harm.[50] More so, if the interests of the current generation can be harmed without their knowledge, it can equally be said that a lack of awareness by future generations does not make it impossible to harm or preserve their interests in their absence.[51] What matters is the harm, not the feeling of being harmed. However, other scholars have criticised intergenerational rights as being too impersonal as they do not appeal to a distinct identity. It is argued that the current approach of intergenerational rights perceives future generations as strangers by adopting an abstract idea of their identity.[52] Vernon has argued that this argument is unsatisfactory as when we speak of intergenerational rights, we protect our descendants' interests because 'they are ours' and hence have a biological identity.[53]

Assuming the proposed analogy is still unsatisfactory, according to John Austin's classification of duties, intergenerational obligations are absolute duties which occur independently of any correlative right.[54] We may therefore conclude that the current generation's responsibilities to future generations are obligations under which no correlative rights exist because there are no identifiable individuals to whom the right applies.[55]Accordingly, the correlation between epidemics and inter-generational obligations is

[48] 'Stanford Encyclopedia of Philosophy' <https://plato.stanford.edu/entries/rights/> accessed 19 May 2021.
[49] Émilie Gaillard, 'The Rights of Future Generations, A New Legal Humanism' *The Agence Francaise De Development* (27 August 2019) <https://ideas4development.org/en/rights-future-generations-legal-humanism/>.
[50] Vernon op cit note 47 at 9.
[51] ibid.
[52] ibid 10.
[53] ibid.
[54] Allen op cit note 31 at 352.
[55] Weiss op cit note 32 at 204.

obvious if inter-generational justice entails improving the life chances and conditions of future generations as much as possible. Epidemics such as TB continue to bring death and suffering to people, and we must protect future generations from this foreseeable harm if it is within our control. The gravity of the TB epidemic serves as a stark reminder that we must address the challenges of intergenerational rights and obligations by practical solutions.

iii. Can intergenerational rights be constitutionalised?

There are several constitutions that mention of rights or interests of future generations.[56] These provisions usually refer to concerns about the environment and sustainable development as a way of safeguarding the interests of future generations. [57] Particularly, Gosseries notes that the reference to future generations in constitutions and legislation tends to be presented through phrases such as 'in the interest of'' or 'for the benefit of', and 'the environment in which will develop.'[58]

Similarly, the South African Constitution incorporates a concern for future generations under section 24. It reads as follows:

> '24. Everyone has the right—
>
> (a) to an environment that is not harmful to their health or wellbeing; and
>
> (b) to have the environment protected, for the benefit of present and future generations, through reasonable legislative and other measures that—
>
> (i) prevent pollution and ecological degradation;
>
> (ii) promote conservation; and
>
> (iii) secure ecologically sustainable development and use of natural resources while promoting justifiable economic and social development.'

The Constitution thereby clearly entrenches a duty on the government to protect the environment for the benefit of future generations. Considering the dating of the Constitution, only environmental matters were of much importance at the time it was drafted largely inspired by UN debates about sustainable development. However, central to African philosophy is the principle of *ubuntu.* The principle of *ubuntu* is also considered to be a major influence on the South African Constitution. It was first mentioned in the Republic of South Africa's Interim Constitution in its postamble. The postamble provides as follows;

[56] Gosseries op cit note 17.
[57] ibid 448.
[58] ibid.

> 'The adoption of this Constitution lays the secure foundation for the people of South Africa to transcend the divisions and strife of the past, which generated gross violations of human rights, the transgression of humanitarian principles in violent conflicts and a legacy of hatred, fear, guilt and revenge. These can now be addressed on the basis that there is a need for understanding but not for vengeance, a need for reparation but not for retaliation, a need for *ubuntu* but not for victimisation.'[59]

The notion of *ubuntu* is now part of South African legal culture although without a union definition. Bennett contends that the absence of a single definition is preferable and avers the following;

> '[A]lthough the law rarely tolerates technical terms with open-ended meanings, certain words are deliberately allowed to remain ambiguous so as to permit judges discretion in applying them to diverse factual situations. Words such as 'wrongful' and 'reasonable' are typical examples. Ubuntu falls into this category. While judges and academics have filled many pages with debate about definition, its meaning in law will persist in remaining fluid.'[60]

Hence, the principle of ubuntu is commonly expressed by the maxim '*Umuntu ngumuntu ngabantu'* (in Zulu) and translated as 'a person is a person through other persons.'[61] Stemming from this maxim, the term ubuntu in its philosophical sense is used to describe the underlying ethos of sub-Saharan African cultures, which maintains that because humans are naturally social creatures, they need other people in order to live fulfilling lives. As a result, community members have reciprocal responsibilities to one another that are intended to promote harmonious coexistence.[62] It is therefore regarded as 'a comprehensive ancient African worldview based on the core values of intense humanness, caring, sharing, respect, compassion and associated values, ensuring a happy and qualitative human community life in a spirit of family.'[63] This underscores the holistic rather than a narrow perspective of which human relationships should be viewed. Put simply, the principle of *ubuntu* recognises the important link between past, present and future generations.[64] Behrens further avers that the theory of

[59] Constitution of the Republic of South Africa Act 200 of 1993.
[60] TW Bennett, AR Munro and PJ Jacobs, *Ubuntu: An African Jurisprudence* (Juta Limited 2018) 3.
[61] Jacqueline Church, 'Sustainable Development and the Culture of UBuntu' [2012] *De Jure* 524.
[62] M Munyuka & M Mothlabi, 'Ubuntu and Its Socio-Moral Significance', *African Ethics: An Anthology of Comparative and Applied Ethics* (ed, 2009) 65.
[63] Leonard Tumaini Chuwa, 'Interpreting the Culture of Ubuntu: The Contribution of a Representative Indigenous African Ethics to Global Bioethics' (PhD, Duquesne University 2012) 2.
[64] Church op cit note 60 at 528–529.

intergenerational justice is compatible with African philosophical thinking, which encourages interdependence in this world and is deeply entrenched in past worlds and future worlds.[65]

There are many interpretations of the African value of ubuntu. Ubuntu has been recognized as a constitutional value, albeit an unwritten one, that is so deeply ingrained in the fabric of society and ought to be protected.[66] In *Port Elizabeth Municipality v. Various Occupiers*[67], the Constitutional Court (CC) succinctly described the influence of Ubuntu as a Constitutional value. The Constitutional Court stated that 'the spirit of ubuntu, part of the deep cultural heritage of the majority of the population, suffuses the whole constitutional order. It combines individual rights with a communitarian philosophy.'[68] The White Paper on Social Welfare also describes the importance of *ubuntu* as follows:

> 'The principle of caring for each other's well-being will be promoted, and a spirit of mutual support fostered.'[69]

This signifies a synergy between values of the most progressive Constitution in the world and the ancient principle of ubuntu. The Constitutional Court's judgment in *S v. Makwanyane*[70] represented the first judicial application of the principle of Ubuntu. In attempts to define Ubuntu, it is common to use Justice Mokgoro's definition of Ubuntu. She states the following;

> 'Generally, ubuntu translates as humaneness. In its most fundamental sense, it translates as personhood and morality. Metaphorically, it expresses itself in umuntu ngumuntu ngabantu, describing the significance of group solidarity on survival issues so central to the survival of communities. While it envelops the key values of group solidarity, compassion, respect, human dignity, conformity to basic norms and collective unity, in its fundamental sense it denotes humanity and morality …. .'[71]

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[65] K Behrens, 'Moral Obligations towards Future Generations in African Thought' (2012) 8(2–3) *Journal of Global Ethics* 179, 179–182.
[66] Clarence I Tshoose, 'The Emerging Role of the Constitutional Value of Ubuntu for Informal Social Security in South Africa' (2009) 3 *African Journal of Legal studies* 12, 18.
[67] *Port Elizabeth Municipality v Various Occupiers* [2004] ZACC 7, 2005 (1) SA 217 (CC).
[68] ibid 37.
[69] Department of Welfare, 'Principles, Guidelines, Recommendations, Proposed Policies and Programmes for Developmental Social Welfare in South Africa.' <https://www.gov.za/sites/default/files/gcis_document/201409/whitepaperonsocialwelfare0.pdf> accessed 10 August 2022.
[70] *S v Makwanyane* [1995] ZACC 3, 1995 (3) SA 391.
[71] ibid 308.

I wish to draw attention to Mokgoro J's expression on the significance of group solidarity to ensure community survival. Ubuntu is a collective philosophy in which the idea of communality, rather than individuality is promoted as the fundamental characteristic of African philosophy.[72] It is therefore evident that the integration of communitarianism as a feature of the Ubuntu translates that collective interests are more important than the individual interests. A communitarian approach to interpretation of section 24 of the Constitution would therefore be acceptable since individualism in its strict sense is a foreign concept in the African way of living. Oyowe highlights a differing perspective that the principle of Ubuntu conflicts with the Bill of Rights due to its communitarian nature.[73] This is attributed to the misunderstanding that rights are individualistic in nature. This is not the case as per Sachs J's assertion in the *Port Elizabeth Municipality* case that Ubuntu consolidates individual rights with a communitarian philosophy. According to Sachs J, the constitutional order blends individual rights with communitarianism, demonstrating that the Constitution does not operate in a liberal vacuum where the focus is exclusively on the individual.[74] Despite the value ascribed to Ubuntu, the aforementioned case law does not make it apparent what Ubuntu requires as a constitutional value. I however suggest that this assertion makes reference to the fact that if ubuntu is in consonance with individual human rights then the pursuit of social justice must be considered in light of ubuntu as a Constitutional value. Ubuntu is a principle that runs through the entire South African constitutional order and that the relationship of interdependence and burden-sharing should also extend across generations.

Against that background, there is no reason why *ubuntu*, which has served as a cornerstone for intergenerational human relations, cannot be applied to healthcare issues. It would therefore not be unfounded to hypothesise that had section 27 of the Constitution — the right of access to healthcare services — been drafted with the spirit of *ubuntu* in mind, the provision could have been drafted in a way that also incorporates health interests of future generations. Healthcare in *ubuntu* culture is communitarian as it is characterised by a sense of shared accountability and community participation.[75] All aspects of communitarianism assume that the government is in charge of providing social protection for its citizens against

[72] I Keevey, 'Ubuntu versus the Core Values of the South African Constitution' (2009) 34(2) *Journal for Juridica*l *Science* 35.
[73] AO Oyowe, 'Strange Bedfellows: Rethinking Ubuntu and Human Rights in South Africa' (2013) 13(1) *African Human Rights Law Journal* 1.
[74] *Port Elizabeth Municipality v Various Occupiers* at para 37.
[75] Chuwa op cit note 63 at 24–26.

risks to their health and safety. The clinical translation of human genome editing as a sustainable way of tackling the TB epidemic is in line with the principle of *ubuntu* as everyone is ontologically linked to the community and thus obligated to care for each other's well-being by establishing the necessary herd immunity through germline editing. As articulated by Tutu:

> *'Ubuntu* … means my humanity is caught up, is inextricably bound up, in theirs. We belong in a bundle of life. We say, 'a person is a person through other people'. It is not 'I think therefore I am'. It says rather: 'I am human because I belong'. I participate, I share. A person with *Ubuntu* is open and available to others, affirming of others, does not feel threatened that others are able and good; for he or she has the proper self-assurance that comes from knowing that he or she belongs in a greater whole, and is diminished when others are humiliated or diminished, when others are tortured or oppressed, or treated as if they were less than who they are.'[76]

Arguments presented in this section could be used to justify a diversity of obligations that the present generation owes to future generations. In essence, the intergenerational justice argument asserts that actions of the present generation that jeopardise the interests of future generations are unjust and should be avoided. Hence, by describing future generations to being current bearers of rights known as intergenerational rights ensures that the current generation does not formulate obligations tailored to favour their own interests at the expense of future generations. The moral choice therefore is to take those actions that increase the welfare of future persons such as human genome editing for the treatment of TB. Interestingly, the Constitution incorporates interests of future generations under section 24. Although, the provision does not speak to public health matters, the Constitution was drafted with the principle of *ubuntu* in mind. As a result, in keeping with the *ubuntu* principle, we must look after the well-being of future generations and protect them from TB by establishing the requisite herd immunity through human genome editing.

II. THE NON-IDENTITY PROBLEM

It is indisputable that in some instances the choices of the current generations affect not only the quality of life but also the identity of future persons. According to the non-identity

[76] D Tutu, *No Future without Forgiveness* (Random House 2009) 34–35.

problem, as popularised by Derek Parfit in the 1980s in his book *Reasons and Persons*, our actions determine which individuals will exist in the future. [77] This presupposition allows Parfit to argue for his time-dependence claim which states that 'if any particular person had not been conceived within a month of the time when he was in fact conceived, he would in fact never have existed.'[78] Put differently, if an individual were born from a different ovum and spermatozoon a month later, this would have been a completely distinct person. The non-identity problem is therefore premised on the fact that our identities are determined by when and how we are conceived. By simply taking time (or not taking time), has a bearing on the identity of the person conceived as time affects which sperm fertilises the egg.[79] Accordingly, the circumstances surrounding one's conception are distinct — they are the only ones that are feasible for him/her — and his/her existence is dependent on them. The non-identity problem, if interpreted in the strictest sense, rules out any chance of harming future generations. The theory presupposes that choosing not to edit the genes of your unborn who is susceptible to being born with some genetic disorder is doing no harm to the child because had the genes been edited, a different child would have been born.[80] Thus being born with a certain disorder is a life worth living as compared to not being born at all.

The non-identity problem has often been viewed as a serious challenge to the theory of intergenerational justice. This concept suggests that failing to employ pre-implantation genetic screening when it is readily available is of no harm to the unborn child. If different gametes had been chosen to exclude the genetic disorder, the resulting zygote would have created a different baby altogether. While adhering to Parfit's non-identity argument, being born with the genetic disorder was the only possible start to life for the child and the parents could not have made it any better by varying the original genetic composition. Therefore, any claims to have been harmed under this concept lie between deciding for a child to be born with a genetic disorder and not existing at all. While on the surface this concept seems to object to the concept of intergenerational justice, it also simultaneously renders gene-editing technology a pretty useless science since in any case a different human would be born. As such, pre-implantation genetic screening and any choice adopted thereof cannot amount to harm as the only state worse

[77] Keyur Doolabh and others, 'Is the Non-Identity Problem Relevant to Public Health and Policy? An Online Survey' (2019) 20(46) *BMC Medical Ethics* 1.
[78] RAJ Mees, 'Intergenerational Justice and Personal Identity: A Contribution to Solving the Non-Identity Problem' (Master's degree, Utrecht University 2010) 11.
[79] Rivka Weinberg, 'Identifying and Dissolving the Non-Identity Problem' (2008) 137 *Philosophy Studies* 4.
[80] A Wrigley, 'Harm to Future Persons: Non-Identity Problems and Counterpart Solutions' (2012) 15(2) *Journal of Ethical Theory and Moral Practice* 176–177.

off than they would otherwise have been is a state of non-existence.[81] This raises questions about the commitments that we believe we have with regard to individuals who, by our own actions, are both led to exist and to have existences that are, albeit worthy, inevitably faulty.

Parfit's line of reasoning draws away from the ethical intuition that certain reproductive decisions harm unborn children. The principle of procreative beneficence instructs prospective parents to select a child that can be expected to enjoy the highest level of well-being. Based on this principle, a parent who is aware of the potential disease a child might be born with should be expected to edit such child's genes to give birth to a healthier child who would be expected to have a better chance of enjoying the most well-being in his life. Julian Savulescu and Guy Kahane defend the principle of procreative beneficence by stating as follows:

> 'According to this principle, "If couples (or single reproducers) have decided to have a child, and selection is possible, then they have a significant moral reason to select the child, of the possible children they could have, whose life can be expected, in light of the relevant available information, to go best or at least not worse than any of the others."[82]

More so, it could also be argued that parents owe it to their potential baby to create a baby who enjoys the greatest amount of well-being among the choices accessible to them. Arguably, germline gene editing can only infringe on the principle of intergenerational justice if the present generation causes future persons to be worse off than they normally would have had the agent not acted differently. Elizabeth Harman has also described the issue as follows;

> 'The non-identity problem concerns actions that affect who exist in the future. If such an action is performed, certain people will exist in the future who would not otherwise have existed: they are not identical to any of the people who would have existed if the action had not been performed. Some of these actions seem to be wrong, and they seem to be wrong in virtue of harming the very future individuals whose existence is dependent on there having been performed. The problem arises when it is argued that the actions do not harm these people because the actions do not make them worse off than they would otherwise be.'[83]

With regard to the scope of accountability to future persons, most philosophers share the view that this theory only extends to the foreseeable future save for limitations on prognostic knowledge.[84] Should we therefore compensate someone for harm done by their forefathers

[81] ibid 177.
[82] J Savulescu & G Kahane, 'The Moral Obligation to Create Children with the Best Chance of the Best Life' (2009) 23 *Bioethics* 274.
[83] Elizabeth Harman, 'Can We Harm and Benefit in Creating?' (2004) 18(1) *Philosophical Perspectives* 89.
[84] Joerg Chet Tremmel, *Handbook of Intergenerational Justice* UK/USA: Edgar Publishing Limited, (2006) 29.

(effects of gene editing) when it can be proved that she would not have existed had the wrong not been done.[85] Drawing from Parfit's theory, one can only ascertain that they were harmed or wronged if the psycho-physical identity of the wronged person is not what it is because the wrongdoing.[86]

This theory adopts the outcome approach in that one can only claim to have been harmed if they are worse off than they already were. Where does this leave the theory in the context of intergenerational justice? Following its strict application, the non-identity problem has no place in any discussion concerning the effects of germline gene editing on future persons. To succeed in claiming harm, the pyscho-physical identity of the person claimant must be fixed between the world as it is and the counter-factual world to which it is being compared. This entails that the person should have already existed at the time the harm was done to be compared to have been taken to a worse-off state. One would therefore wonder who the actual beneficiaries of this theory are if it has no relevance to future persons. Perhaps it can only be applied to the present generation who undergo gene therapy and are made worse off than they already were. The non-identity problem therefore raises concerns about popular intuitions as to who can be wronged.

Therefore, the non-identity problem is a significant moral quandary that is becoming more important as it raises issues that have largely shaped the philosophical discussion of intergenerational justice.[87] In such cases, the non-identity problem poses issues about the commitments we believe we owe to persons, who as a result of our own actions, are caused to have existences that is flawed. The difficulty emerges when the individual whom an activity appears to harm would never exist if it were not for that action, as described by Derek Parfit.[88] Put differently, had the circumstances been different, a different person would have been born. As a result, the non-identity problem probes us to consider to whom exactly our actions make one better or worse off as such person would not have existed had circumstances changed.

Realistically, many of our acts may, in one way or the other, alter the identity of future individuals. What really raises moral concerns in non-identity cases is altering the identity in a way that impacts the wellbeing and quality of life of these future individuals. According to a

[85] Melinda A Roberts and David T Wasserman, *Harming Future Persons: Ethics, Genetics and the Non-Identity Problem* (Springer Dordrecht Heidelberg 2009) 5.
[86] R Kumar, 'Who Can Be Wronged' (2003) 31(2) *Philosophy & Public Affairs* 99–101.
[87] Jared Scott Reichert Thomas, 'A Capabilities Approach to the Non-Identity Problem' (Research project, Claremont McKenna College 2014) 6.
[88] Thomas Bontly 'Causes, Contrasts, and the Non-identity Problem' (2016) 173(5) *Philosophy Studies* 1234.

popular response to the non-identity problem, existence must have a negative quality for non-existence to be preferable'.[89] On that account, it is possible that although germline editing could be seen as advancing the best interests of the child when employed for therapeutic purposes, it might equally be seen as jeopardising the welfare of the future child where the effects of germline editing are so unbearable that non-existence is preferable.[90]

In the case of *AB v Minister of Social Development,*[91] the Constitutional Court was tasked with striking a balance between the parents' rights and those of the prospective child. In this matter, an infertile woman was barred from employing surrogacy because she could not contribute her own eggs for the surrogate child's conception. This was because South African statutory law requires a commissioning parent to use her own gametes. She contended that this requirement violated, amongst others, her reproductive rights. In opposing the application, the Minister of Social Development relied on the child welfare principle and argued that knowing one's genetic origins is in the best interests of children. Interestingly, since there was no actual child in existence at that point in time, the Minister effectively postulated that the child welfare principle should be extended to the prospective child.[92] Over and above that, the majority of the Constitutional Court ruled that the Court must indeed protect the prospective child's best interests.[93] Although the *AB judgment* did not explore what exactly constitutes harm to the prospective child, Thaldar and Shozi argue that the concept of harm to a future child should be viewed as an anticipated future event. That is, a harm that will only manifest and affect the child once he or she is born.[94]

In *Ex Parte KAF*[95], the Court drew a distinction between embryos and the mental construct of the potential child. Therefore, the Court was not required to take into account embryos' best interests as a potential offspring. Thaldar and Shozi hence argue that embryos should not be regarded of as future children but rather as biological material and as such 'there is no continuity of identity between any particular in vitro embryo and the identity of the person who is born utilizing that embryo.'[96] Therefore, selecting one of two embryos would not involve choosing between two offspring as either embryo can result in the same mentally constructed

[89] Donrich Thaldar & Bonginkosi Shozi, 'Procreative Non-Maleficence: A South African Human Rights Perspective on Heritable Human Genome Editing' (2020) 3(1) *The CRISPR Journal* 34.
[90] ibid.
[91] *AB v Minister of Social Development* 2017 (3) SA 570 (CC).
[92] Thaldar and Shozi op cit note 83 at 33.
[93] ibid.
[94] ibid 34.
[95] *Ex Parte KAF* (2019 (2) SA 510 (GJ)).
[96] Thaldar and Shozi op cit note 89 at 35.

prospective child.[97] Consequently, harm to future persons caused by germline editing can only materialise once they are born and experience some degree of suffering as a result of it. They suggest the following rule:

> 'If a reproductive decision by a prospective parent is likely to have an effect on the prospective child that would constitute either a civil or criminal wrong in law if caused by an act by a parent toward an existing child, such reproductive decision would constitute harm to the prospective child.'

The Constitutional Court in the case of *H v Fetal Assessment Centre*[98] also steered away from the notion that one's quality of life must be worse than non-existence to constitute harm from an act that was performed before birth. In this case, a boy duly assisted by the mother sued the Fetal Assessment Centre for damages stemming from the centre's failure to notify his expectant mother of the high likelihood of him being born with Down Syndrome. He claimed that if his mother had known about the risk, she would have terminated the pregnancy. The High Constitutional Court (CC) dismissed the claim, stating that wrongful life claims[99] are not recognised under South African law. Under the current law, only parents can seek compensation for financial losses incurred as a result of the increased costs of caring for a child with disability — wrongful birth claim. On appeal, the Constitutional Court found that the child's claim — wrongful life — could exist in our law and will have to be considered in accordance with Constitutional principles including the right to have the child's best interests regarded.[100] As a consequence, the appeal was successful in the sense that the CC ruling afforded the child with a window of opportunity to file for a claim for compensating a life with disability.

Although the CC did not address the non-identity problem explicitly, this reflects the non-identity problem because it compares the child's current position and what position the child would have been if not for the medical mistake. That is, a comparison is being made with what could have been a child without Down Syndrome and not the boy's non-existence. Thus, being born with Down Syndrome is certainly not the best but it is a life worth living as compared to not being born at all. More so, the mere fact of considering the possibility of such claims by

[97] ibid.
[98] *H v Fetal Assessment Centre* 2015 (2) SA 193 (CC).
[99] The Supreme Court of Appeal (SCA) has defined a 'wrongful life' claim as 'an action brought by a deformed child, who was born as a result of negligent diagnosis or other act by a doctor. See *Mukheiber v. Raath* [1999] 3 All SA 490 at para 1.
[100] *H v Fetal Assessment Centre* at paras 42,49.

the CC is an acknowledgement that it is in fact still the same person bringing the claim and not a different person as suggested by the non-identity problem. Furthermore, even though the CC's consideration of the wrongful life claim was primarily theoretical, this judgment opened doors for potential claims in the future and of which lower courts simply cannot ignore the CC's analysis.[101] Put differently, the occurrence of wrongful life claims clearly demonstrates that the non-identity problem is not necessarily a philosophical issue left only in the hands of philosophers; it also reflects the real dilemma some people (like wrongful life plaintiffs) faced in real life. Consequently, should prospective children believe that they were legally harmed by the editing of their genomes before birth, then the CC has opened the door to the possibility of the prospective child instituting a wrongful life claim, provided such child is able to satisfy all the normal requirements.

The above literature highlights that issues of intergenerational concerns can be cast as broadly as the imagination allows. It has advanced arguments why generational rights should be regarded as human rights. As far as the South African position is concerned, the non-identity problem has potential of dwindling or halting the clinical application of human genome editing. The existence of wrongful life claims clearly indicates that there are voices to be heard in reality. More so, the fact that the CC has potentially opened its door to a wrongful life claim reflects the reality that children with serious and painful conditions as a result of the use of human genome editing could be compensated to improve their living circumstances (or, to put it another way, to make their existence more acceptable and comfortable). However, although we have a responsibility to future persons, we ought to desist from unnecessarily creating a panic that human genome editing could affect 'all' prospective future persons to necessarily be worse off. The legally relevant comparison is between the future child's quality of life with a life of unedited genomes which is something that currently remains hypothetical, and therefore the over-reliance on anticipatory harm that may never materialise should be avoided.

[101] P Mahery, 'A Child's Potential Claim for Negligent Misdiagnosis: The Case of H v Fetal Assessment Centre' (2016) 106(4) *South African Medical Journal* 349.

CHAPTER 6

CONCLUSION

'When you are studying any matter, or considering any philosophy, ask yourself only what the facts are and what is the truth that the facts bear out. Never let yourself be diverted either by what you wish to believe, or by what you think would have beneficent social effects if it were believed. But look only solely at the facts.' **— Bertrand Russell**

I. INTRODUCTION

The narrative began in 2018 when He Jiankui, a Chinese researcher, after utilising CRISPR technology, reported the birth of Lulu and Nana, the world's first germline modified babies.[1] He Jiankui reported to having edited the embryos so that the children would be born HIV-resistant.[2] Although the announcement was met with widespread disgruntlement of his behaviour, the fact remains, we are now living in the CRISPR-era, and it seems obvious that the field of human genome editing could drastically transform in the coming years.

In order to achieve the End TB vision, there is need for substantial improvements to the efficiency of the current TB control interventions. This thesis tells a story about the potential development and use of CRISPR CasX as a potential solution to emolliate the current TB epidemic with which South Africa is challenged. It also reveals an older story about the normative interpretation of the right of access to healthcare services as enshrined under section 27 of the South African Constitution and how the right to human genome editing can be said to fall within its ambit.

Against the backdrop of emerging human genome editing technology, the main aim of this study was to analyse whether the South African Constitutional right of access to healthcare services includes the right to human genome editing technology for the treatment of TB. Under objective 1, the study aimed to analyse the right of access to health care in the context of access to human genome editing. Under objective 2, the study investigated the instrumental value of

[1] Henry T Greely, 'CRISPR'd Babies: Human Germline Genome Editing in the "He Jiankui Affair"' (2019) 6(1) *Journal of Law and the Biosciences* 111, 110-111.
[2] ibid 112.

the right to science to enhance access to health technologies such as human genome editing. Objective 3 analysed how the rights of the present generation wanting access to human genome editing may be properly balanced with those of the future generation. The final objective was to investigate the current international trends in applying the precautionary principle in the regulation of human genome editing and how South Africa should proceed to apply the precautionary principle.

In addressing these issues, this Chapter will therefore offer the conclusion based on this thesis' main themes as discussed per chapter.

- The right to freedom of scientific research and human genome editing
- Human genome editing and the precautionary principle- responsible translational pathway for human genome editing
- The application and ambit of the right of access to healthcare services
- Human genome editing and the health of future generations

II. CHAPTER SUMMARIES

This study analytically situates the right to science and the right of access to healthcare services as the centre of human rights necessary to promote access to the needful gene-editing technology. Chapter 2 discussed the right to scientific research as this places a constitutional limit on the powers of the government to unnecessarily restrict the development of this novel technology. The chapter identifies that, despite its legally binding nature, the observance and enjoyment of the right to scientific research is short-lived as the Constitution does not explicitly recognise the right to enjoy the benefits of such scientific progress although the broader right to science as recognised in the UDHR entails both the right of scientists to freely conduct science and to have the results of their work protected and the right of individuals to access and enjoy the benefits of scientific advancement. Consequently, promoting scientific research is ineffective, especially if society is not guaranteed the right to benefit from such scientific advancement and its applications. Society is denied the benefit of access to new disease treatment methods such as human genome editing. The chapter discussions revealed that heritable human genome editing basic research is permitted, however South African legislation prohibits the creation of embryos for research purposes and enforces the fourteen-day rule. This demonstrated that while South Africa's framework is not highly restrictive, it could be more permissive in terms of the creation of embryos for research. In doing so, the safety and efficacy

concerns posed by CRISPR-CasX as raised in Chapter 1 could potentially be invalidated through further heritable human genome editing research beyond the 14-day rule. Furthermore, in advancing the clinic application of CRISPR therapies, the chapter discussed the possibility of having germline editing clinical applications fall within the regulatory ambit of the Medicines and Related Substances Act. Discussions therein revealed that CRISPR therapies could be described as a medicine as per the definition of the Act. Also, various gene editing delivery methods could be explored to ensure that germline editing qualifies as something that is used *in humans* therefore falling within the regulatory scope of the MRSCA.

Chapter 3 discussed the application of the precautionary principle on the clinical translation of gene-editing technology. The study revealed that the precautionary principle, although expressed in multiple formulations, is enshrined in numerous international agreements. Due to the numerous formulations of the precautionary principle, there have been uncertainty and conflicting regulatory decisions. This chapter highlighted that each formulation of the precautionary principle shares key components, which together make up the essence of the precautionary principle and these important factors help determine what, in general, proper implementation of precaution entails. However, the presence of numerous formulations of the principle may allow for a variety of interpretations which may ultimately create high levels of uncertainty on which pathway the global regulation on human genome editing should take. With the weak formulations of the precautionary principle being highly pragmatic, I suggested that this would seem a more workable solution for South Africa as policy makers will have more leeway when it comes to deciding how various conflicting rights and interests should be balanced. It is in this chapter that I proposed a version of the precautionary principle that best serves South Africa's healthcare needs while minimising harm to its people.

Chapter 4 revealed that the right of access to healthcare services as enshrined in the Constitution is enunciated in ambiguous terms as it does not define the quantity or quality of healthcare services to be accessed. As such, Chapter 4 examined the nature, content and legal implications of the constitutional right of access to healthcare services. The chapter also investigated its (non-)realization by inquiring how the Constitutional Court (CC)s have interpreted the normative content of the right and addressed its attendant controversies. Thus, this chapter discussed the theoretical and moral basis for linking access to CRISPR therapies to the right of access to healthcare services and conceptualises the claim for access to gene-

editing technology as falling within the ambit of the right of access to healthcare services. The chapter undraped that the constitutional right of access to healthcare services generally provides a legally binding normative framework within which the clinical translation of human genome editing in South Africa should be pursued.

Chapter 4 advanced the argument that the right of access to healthcare services is an empty promise if there is no practical access such services. Similarly, the right of 'access' does not necessarily mean that the South African government must offer the CRISPR therapy in question but rather, the government must ensure that CRIPSR therapies are reasonably accessible and inexpensive. Furthermore, more than any other accessibility-related challenge, the anticipated cost challenge of CRISPR therapies is concerning especially since the South African healthcare system is already under strain. Access to CRISPR therapies therefore causes us to consider issues of fairness and distributive justice across the different layers of the society. The chapter considered the possibility of rationing and priority setting in healthcare since initial CRISPR therapies are most likely to be available in limited quantities. Although the South African healthcare system has and continues to practice the rationing of healthcare services, the emergence of human genome editing calls upon the government to decide on which category of citizens to prioritise for TB treatment using CRISPR therapies.

In Chapter 5, I comprehensively investigated whether future generations should be given a say in deciding whether the current generation should pursue human heritable genome editing. The findings in this chapter also revealed that although it is theoretically convincing to conceive future generations as having rights, this must be approached with caution, as its arbitrary application can inhibit clinical translation of CRISPR therapies due to concerns about future generations being treated unjustly. Specifically, Chapter 5 showed that, although the non-identity problem poses issues that ultimately have a large bearing on the philosophical discussion of intergenerational justice issues, the South African position may somewhat be different. The case of *H v Fetal Assessment Centre* has demonstrated that despite having a responsibility towards future persons, the morally relevant comparison in wrongful life claims should be to compare the future child's quality of life with a life of unedited genomes (in a case of human genome editing) and not non-existence as postulated by the non-identity problem. Consequently, since harm to future persons caused by germline editing can only materialise once the child is born and experiences some degree of suffering as a result of it, the non-identity problem poses to be a cul-de sac as far as the South African position is concerned.

III. OVERVIEW OF KEY FINDINGS

These objectives together demonstrate that the right of access to healthcare services is an important avenue for demanding access to new TB treatment methods. The findings of objective 1 as explored in Chapter 4 demonstrate that the constitutional right of access to healthcare services generally provides a legally binding normative framework within which human genome editing can be pursued in South Africa. A major strength of this research is its hyper-local context. While there is increasing interest in promoting human genome editing at global level, there has not been much research done to promote access to human genome editing for treatment the of TB in a South African context. Research at this geographic level therefore gives a broad context to the TB epidemic but also equally suggests locally appropriate interventions. By using detailed local epidemiology, the study described how social determinants of TB as well as genomic information play a role in TB risk and treatment outcomes. An instrumental value of promoting the right to scientific research in this setting as per the study's objective 2 would therefore be that further understanding of these risk factors is critical in advocating for TB control interventions that are being omitted by current treatment methods such as human genome editing

Furthermore, another key finding of this thesis is that although the precautionary principle as a risk management tool is expressed in multiple formulations, this study suggested that the weak formulations of the precautionary would be a more workable solution for South Africa as policy makers will have more leeway when it comes to deciding how various conflicting rights and interests should be balanced. In assessing how rights of the current generation may be balanced with the interests of the future generation, the findings of objective 3 demonstrate that although it is theoretically convincing to conceive future generations as having rights, this must be approached with caution so as not to stifle the clinical translation of CRISPR therapies.

IV. FUTURE DIRECTIONS

This thesis has revealed a number of difficulties in respect of the regulation of human genome editing both at global and national level. In recognising that the South African policy on human genome editing is currently unclear, it is hoped that future research will build upon some of the findings in this thesis, and that the recommendations presented here will serve as a catalyst of

a lengthy road towards properly dealing with the plethora of regulatory uncertainty and/or ethical concerns regarding human genome editing in South Africa. South Africa's major challenge will therefore be to promote legislative reform to bridge the gap between law and reproductive technologies while keeping up with the rapid technological advancements.

Most importantly, for human genome editing to progress for the benefit of all and for South Africa to fully reap the benefits of this genetic revolution, innovation must be fostered. It is a common criticism of the precautionary principle that the adoption of a strong formulation operates as a barrier to innovation. As a logical consequence, we can anticipate that adopting a weak or moderate formulation in South Africa will encourage innovation by ensuring that pharmaceutical companies have the right regulatory framework in which innovation and commercialisation of their CRISPR pharmaceuticals would thrive. Despite a variety of actors, institutions, and economic pressures, both within and outside a State, have the power to limit a government's ability to make independent policy decisions, the State should always be viewed as a gatekeeper in the CRISPR market's pathway, which means that the State has the institutional backing to adopt a version of the precautionary principle that advances clinical translation of CRISPR therapies after considering the fundamental human rights at stake and the competitiveness of the technology.

Finally, in formulating the regulatory mechanisms, there is also a need to ensure that the broadest possible demographic variety have equal access to this technology so as not to exacerbate unjust discrimination. Non-discrimination calls for the inclusion of persons who will have financial constraints in accessing these therapies. We must always be bear in mind that TB is the archetypal disease of poverty and the financially vulnerable members of the society need to be protected the most. It is hoped that the rolling out of CRISPR therapies will adhere to principles of equity and justice. This will also ensure that a genetic underclass does not become a reality in South Africa and perpetuate the existing forms of equality.

V. CLOSING REMARKS

Overall, human genome editing using CRISPR-CasX is a promising technology for improving TB care and management in South Africa. During my PhD research, I discovered that despite the substantial investments and efforts to reduce TB incidence, the prevailing TB drug resistance is a major concern to the fight against TB. Studies have not only revealed how TB strains have mutated and spread over time, but also the potential clinical and epidemiological benefits of human genome editing in high-burden countries like South Africa.

With the current advances in CRISPR sequencing, future studies are needed to provide a deeper analysis on the genetic basis for TB pathogenesis, transmission, and drug resistance evolution, as well as CRIPSR's potential applicability in clinical and public health settings. It is hoped that this PhD study will promote a 'bench to bedside' translational research, which will eventually lead to the development of CRISPR therapies for the treatment and prevention of this devastating disease — TB.

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